DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CURRENT GOOD MANUFACTURING PRACTICES REGULATION AND GUIDANCE FOR PET DRUGS

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9:00 a.m.

5630 Fishers Lane, Room 1066
Rockville, Maryland

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C O N T E N T S

P R O C E E D I N G S

Opening Remarks

AXELRAD: I am Jane Axelrad. I am the Associate Director for Policy in the Center for Drug Evaluation and Research and the Chair of the PET Working Group that has been charged with implementing the Food and Drug Administration Modernization Act provisions on PET.

This is the latest in a series. We have had several meetings on implementation activities working with people in the community on developing the regulations that are required under the statutory provisions. It has been quite some time since we have gotten together on this, largely because of the logistics in terms of developing the document and getting it cleared.

We had a change in administration. A whole new set of people came in and, for a while the entire regulatory process was suspended while the new administration took over and it took a while before they began clearing documents again.

Anyway, we have now published the latest Preliminary Draft Proposed Rule on Good Manufacturing Practices and an accompanying guidance document. We are looking forward to

talking with you today and getting your comments and thoughts on how to improve the document so that we can go forward and actually issue a proposed rule and a draft guidance document.

The first thing I would like to do is have everybody at the table introduce themselves. Then I am going to invite people to give opening remarks. If anyone at the table or in the audience would like to make an opening statement, they are welcome to do that.

Then we are going to have a very short presentation from one of our staff who is going to describe how the rule has evolved, sort of the chronology and how we have gotten to where we are today, particularly how we have responded to some of the concerns that were raised at the last meeting that we had on good manufacturing practices.

Then, finally, we are going to start discussing. We will start with the rule and then with the guidance documents and the topics are listed at the second page of your agenda and we will try and sort of follow the outline through.

So, with that, I am going to turn to the people on this side of the table and ask them to

each introduce themselves.

URATANI: Brenda Uratani, Office of Compliance, FDA.

COOPER: Jim Cooper. I have been contracted to advise on the guidance. I am from the Medical University of South Carolina in Charleston.

PENDLETON: Brian Pendleton with CDER's Office of Regulatory Policy.

KASLIWAL: I am Ravi Kasliwal. I am Chemistry Reviewer in the Office of New Drug Chemistry located in the Division of Medical Imaging and Radiopharmaceutical Drug Products in FDA.

LEUTZINGER: I am Eldon Leutzinger. I am the Chemistry Team Leader in the Office of New Drug Chemistry and I serve in the Division of Medical Imaging and Radiopharmaceutical Drug Products.

LOVE: Patricia Love, Division Director, Medical Imaging and Radiopharmaceutical Drug Products.

BARRIO: I am George Barrio from UCLA and Chair of the committee representing the Academy of Molecular Imaging and Society of Nuclear Medicine.

KEPPLER: Jennifer Keppler with the

Academy of Molecular Imaging.

ZIGLER: Steve Zigler with PET Net.

FERRIS: Bob Ferris with Tyco Healthcare Mallinckrodt.

SWANSON: I am Dennis Swanson, University of Pittsburgh.

CONTI: Peter Conti, University of Southern California. I represent the Government Affairs Council for the Society of Nuclear Medicine.

HUNG: Joe Hung from Mayo Clinic. I am also representing the American Pharmaceutical Association.

AXELRAD: Let me turn to Dr. Barrio if he has some opening remarks.

Opening Remarks from Interested Groups

BARRIO: I would like to thank the agency again for giving us the opportunity to review this new set of CGMPs and guidance. I don't remember how many meetings we have had but we have really had many, and we have discussed this topic many times. In this particular case we have had the opportunity to have the documents on the web and, therefore, all of us really were able to read the document and criticize the document and certainly,

hopefully, make comments, constructive ones, in order to move forward.

We have consulted, of course, our own group. We have gone through many scientists, physicians, practitioners, pharmacists, and there is a unanimous feeling that this guidance and CGMP documents are clearly geared for radiopharmaceuticals in clinical use. I think there are issues that we will be discussing here, clearly, related to the practice of pharmacy, medicine and many other things, but I think one important issue that I would like to indicate that is pertinent to the future of the field is that this document, as such, contains significant elements that are, indeed, non-applicable to research situations. For example, we need to understand how RDRC protocols or IND protocols or even clinical trials and their INDs can be subjected to this kind of regulation. I think just looking at the document, it looks a little frightening from that perspective.

These requirements are not necessarily, of course, related to the quality of the radiopharmaceuticals that we will be injecting in humans. This is never an issue and will never be

an issue. We, in the community, are all in complete agreement that our patients or human subjects in research should receive the best radiopharmaceuticals that we can ever produce. But I think we are concerned about requirements of documentation, tracking, testing, preparation of synthesis system, many of these issues that can be appropriate for manufacturing in an industrial environment and, clearly, the opinion of the committee was that they are not really suited for a research environment in academia.

Then, I think we have had great success with the FDA in the past, working together with USP and the community to frame the U.S. Monograph and the general chapter. That was a very, very successful experience. We all feel that. I think that model, we would like to suggest, can be used effectively again to assist the agency to produce a more appropriate guidance to cover all the situations.

AXELRAD: Does anyone else at the table want to make an opening statement? Dr. Hung?

HUNG: Again, I am representing not only the Mayo Clinic but also APhA. I assume you know I have been pretty vocal about the issue on the

component PET drug, and I believe it should not be subject to CGMP and ANDA regulations.

But let's put that aside and just look at the current proposed guidance, and I have to congratulate the members of the PET steering committee of the FDA. You have done a wonderful job. I think you have shown some common sense and flexibility in dealing with so many difficult issues. I have realized that there is never going to be a guidance that is going to satisfy everyone, and I submitted my comments to the FDA on April 29th.

I just want to mention a couple of issues that I mentioned in the letter. One is that I don't know how the FDA is going to deal with the issue in terms--I know the guidance tried to be very flexible but, on the other hand, it is pretty vague. So, I don't know how the agency is going to deal with the issue in terms of how to define size of PET centers, how do you define small versus large, and the air quality, that kind of stuff. So, are you going to be depending on the inspector to define those issues?

The other thing is I think in the guidance it mentions that the quality control unit should be

separate from the production unit. I don't know the agency's view on that. Should there be a group of people that is separate from the production group so that they can not be involved in the production function on a daily basis? If that is the case, I think it will create a lot of problems because, as you know, there is a shortage of qualified people in this particular field. So, if you are going to have an independent quality control unit to do that type of quality control function and cannot be involved in the production, I think we are going to have a problem there.

Also, there are a couple of issues about the new document such as NRC which is going to issue a new Part 35, and the USP already issued the 25th edition. So, those kind of need to be updated in the guidance.

Those are some issues that I already addressed in my letter to the FDA. So, I don't want to take up too much time but overall I think it is a very good document, very flexible, but I think we need to be more specific. Unfortunately, for this kind of issue you want to be flexible and you want to be specific, so I think this will be kind of an important issue to be discussed at this

meeting today. Thank you very much.

AXELRAD: Is there anyone in the audience who would like to make an opening statement? Come on.

CARETTA: Good morning. I am Dr. Bob Caretta, and I am representing CORAR, the Counts on Radionuclides or Radiopharmaceuticals, and we would like to make an opening statement to the committee.

CORAR agrees with the FDA's conclusion that all PET centers should be subject to CGMP. Section 121 of the FDA Modernization Act provides that the FDA must take into account any relevant differences between not-for-profit institutions that compound PET drugs for their patients and commercial institutions. FDA has correctly determined that not-for-profit or commercial status is not relevant to the processes and controls that are necessary to produce safe and effective PET products. Many not-for-profit medical centers are producing PET drugs on a large scale, larger than many independent commercial PET centers. In certain cases, these academic centers are not only producing drugs for their own patients but selling to other institutions as well. There is no justification for exempting these large volume

not-for-profit producers from CGMP while commercial centers of similar, or smaller, size are required to comply.

Moreover, as FDA has recognized, not-for-profit medical centers are increasingly using for-profit commercial firms to operate their PET centers on site. This is a growing trend that blurs the distinction between for-profit and not-for-profit centers. There is no rational reason why a not-for-profit medical center that retains a commercial contractor to operate its PET center should be required to comply with CGMP while a neighboring not-for-profit institution that operates its own center should be exempt.

FDA's mandate is to ensure that all patients receive PET drugs of appropriate quantity, quality and potency, thus assuring safety and efficacy regardless of the commercial status of the PET center. The preliminary draft rule achieves this by defining the PET centers subject to CGMP to include all facilities engaged in the production of PET drugs. A patient should not be subject to the greater risk of product adulteration, instability, contamination or subpotency merely because he or she is being treated at a not-for-profit medical

center.

Although CGMP properly applies to all PET centers, CORAR believes that there should be flexibility that prevents small centers, with limited resources, from having to meet CGMP requirements that are unduly burdensome. We believe that the draft guidance provides this flexibility by taking into account the reduced staffing levels and space concerns of smaller PET centers. For example, with appropriate procedural controls small PET centers can combine production and quality control functions. A PET center that produces a few daily doses of a PET drug may use two persons or in some cases the same individual to accomplish all production of quality control functions. As another example, small centers can use self-checks instead of second person checks on production laboratory quality control steps. Also, in small PET centers the same area room can be used for multiple purposes, for example, production, laboratory operations and component storage.

In summary, CORAR believes the preliminary draft rule and draft CGMP guidance strikes a proper balance by requiring CGMP compliance for all PET centers, yet providing flexibility in the

application of the CGMPs to accommodate small centers.

I would like to make one other comment that is a concern of CORAR. The area of the draft guidance that needs to be clarified is the distinction between PET drug production and the practice of pharmacy. The draft guidance states that PET drug operations subject to CGMP would include all operations to the point of final release of a finished dose form, and subsequent use of a drug product is part of the practice of pharmacy or medicine. A parenthetical explains that finished dosage form includes unit dose containers, multiple dose containers and pharmacy bulk packages. In the frequent situation where a PET drug as finished bulk solution is released from a PET producer to a nuclear pharmacy, which then draws the solution up in calibrated unit dose syringes, it is unclear from the guidance whether the finished dosage form would be the bulk solution or the unit dose syringe. If the latter, a nuclear pharmacy would be subject to CGMP for engaging in activities that traditionally have been considered part of the practice of pharmacy. In the past FDA has not considered a finished dosage form necessary

to be packaged in the final container, but the guidance suggests otherwise. CORAR urges FDA to clarify how the PET CGMP would apply in this situation. Thank you for your time.

AXELRAD: Thank you very much. Is there anyone else who wants to say anything? Let me just say that certainly you will notice from the agenda that the issue of CGMP applicability to PET drug production and the practice of pharmacy and this issue of where you draw the line is the first thing on our agenda. So, what we would like to do now is have Brian Pendleton, from the Regulatory Policy staff, give a little bit of an overview of the regulation and the guidance, and how we have addressed some of the concerns that were brought up the last time. Then we will get right into the discussion of the rule and specifically the first item on the agenda is where do we draw the line.

I would also like to say that, unfortunately, we have grown. When we first started doing these meetings I think there were probably five people in the audience. So, we were able to have a very free-flowing dialogue. We have sort of gotten to the point where we now sort of have to have a formal table. I would like to try

and keep it as informal as possible. I would like people in the audience to be able to comment. I will have to sort of keep some control so that we can make sure that we keep on the schedule and cover the issues, but I would really like to give everybody in the audience who wants to speak an opportunity to do that. So, I think the way we will do it when we get into the documents is introduce a topic and maybe have someone here say a few things, and then open it up and let people at the table first and then anybody else who wants to comment on the issue make remarks because I think it is really important that we get everybody's views on the record. We will respond and have a dialogue as best we can and, of course, then we will go back and take a look at the transcript and determine where to go next.

Also, I wanted to point out that there is an opportunity for written comments. In addition to using the remarks at this meeting, we would really like people who have specific written comments to submit them for the record. I think June 5th is the due date for those. With that, I am going to turn it over to Brian.

FDA Approach to PET CGMP (Overview)

PENDLETON: Thanks, Jane. Good morning. I am pleased that there seems to be some support for our general approach, particularly with respect to clinical use. I was a little concerned that I might feel like I was serving roast beef to a group of vegetarians.

PARTICIPANT: You are.

[Laughter]

PENDLETON: I am!

[Slide]

This is a brief summary of what I am going to be talking about, the overview of our approach at this point to PET CGMP. I am going to briefly talk about the chronology of events leading back to the Modernization Act in 1897.

I am going to give a very brief overview of the draft proposed rule. I am going to talk about some of the differences between proposed Part 212 for PET CGMP and the CGMP regulations in Part 210 and 211 for conventional drugs. I am going to give a very brief overview of the draft guidance. I will let Brenda and Ravi and others handle most of those issues there. I am going to talk about our response to some of the issues that were raised in the 1999 preliminary draft regulations, and the

response that we issued last month along with the draft guidance and the draft proposed rule. I am going to touch on some of the other changes that we made to the 1999 regulations, and talk about some next steps from here.

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As you know, the Modernization Act directed us to develop approach approval procedures and CGMP requirements for PET drugs, and we have had a number of public meetings to discuss them and, of course, last month we issued the draft proposed rule and the draft guidance on PET CGMP.

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The preliminary draft proposed rule contains a revised version of the draft regulations, the codified form, and there is a preamble which explains some of those provisions in a little bit more depth and discusses some general issues. The draft guidance provides more details about some of those provisions and recommendations on how different PET centers can comply with the regulations once they become final. Of course, the guidance is not binding on either the PET community or the FDA, and any final guidance wouldn't be binding either. If you had a way which you felt

was consistent with the Act and the regulations you could institute that.

[Slide]

I just want to touch on some of the important principles that we tried to incorporate into the draft proposed rule. We tried to design to accommodate both not-for-profit academically oriented institutions as well as the larger commercial producers. We tried to incorporate some principles from the USP General Chapter 823 on compounding of radiopharmaceuticals for PET.

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We think there are a number of important differences between the CGMP requirements in Parts 210 and 211 and what we propose for Part 212. There are fewer required personnel, with fewer organizational restrictions. We are allowing for multiple operations or storage in the same area. There are streamlined requirements for aseptic processing. There are streamline quality control requirements for components, as well as specialized QC requirements for PET drugs that are produced in multiple sub-batches.

The draft proposed rule allows for self-verification of significant steps in PET drug

production. It allows for same person oversight of production, of batch record review and product release, and there are more simplified labeling requirements.

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The draft guidance, as I mentioned, provides guidance to the PET community on what would be acceptable approaches to complying with the proposed regulations, and it makes different recommendations for PET centers for how to comply based on the size, scope and complexity of the operations at a particular PET center. It makes recommendations on pretty much all aspects of CGMP, including resources, controls and documentation.

It also provides examples of methods and procedures that different type of PET centers could use to meet the regulations once they are adopted. It discusses a variety of different kinds of equipment and how they can be controlled. It talks about how to test certain components that yield an active pharmaceutical ingredient. It makes recommendations for microbiological controls for aseptic processing. So, it provides a number of examples in these types of things.

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As Jane mentioned, we issued a document and put it on the web last month. We tried to address some of the very significant issues that emerged from the discussions on the 1999 preliminary draft regulations, as well as a big issue that emerged at the public meeting in March of 200.

[Slide]

One of the biggest was that the PET community did not like the designation of PET centers as manufacturers or industry. Generally you don't regard yourselves, for the most part, as manufacturers because of your location within academic institutions and the fact that you produce drugs in-house for patients, and we have tried to eliminate all references to manufacturers and industry and replace that with PET drug producers and PET drug production. So, if you see something there that is an inappropriate reference to a manufacturer, manufacturing or industry, please let us know.

[Slide]

Another of the biggest issues was the issue of not-for-profit institutions versus commercial manufacturers. The Modernization Act

directs FDA to take due account of any relevant differences between not-for-profit institutions and commercial manufacturers. Over the past year, year and a half and beyond that, we have examined several PET centers and we think that CGMPs are related primarily to the size, scope and complexity of a PET center's operations rather than a not-for-profit status per se.

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We don't think that not-for-profit status appears to have a significant bearing on either the drugs that are administered to patients or the facilities and procedures that are needed to ensure the quality of those drugs. So, we tried to develop regulations that are flexible enough for all types of PET centers and the guidance, of course, as I mentioned, offers different recommendations depending on the size and scope of operations at PET centers.

For example, with respect to personnel, the draft guidance says that a PET center that only produces a few doses daily one to two people might be adequate for all production and quality control functions. Regarding facilities, it states that in centers with very complex operations separate areas

might be appropriate for different functions. Even though the regulation doesn't require it, in some cases it might be appropriate to actually use separate areas.

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Another important issue, as was touched on earlier, is where PET drug production ends and the practice of pharmacy begins. We did address this in the draft guidance and our view is that FDA-regulated production ends at the final release of the finished drug product. After a drug is received at a facility for administration to patients, everything beyond that point becomes the practice of pharmacy and the practice of medicine that is subject to state and local, not federal, law. Distribution to the receiving facility is covered under CGMP but it would not normally be the focus of inspection unless we learned of a particular problem that was occurring during distribution.

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Another important issue was that PET centers might have to conduct ID testing of all components. The draft proposed rule addresses this by stating that ID testing is only required on each

lot of a component that yields an API and each lot of an inactive ingredient. So, testing of reagents and solvents isn't mandatory under the draft proposed rule. If you are using as an inactive ingredient a product that is marketed as a finished drug product, intended for IV administration, then you don't have to conduct an ID test on that inactive ingredient.

[Slide]

A related issue are some of the conditions that we had proposed in the 1999 draft regulations on using a supplier certificate of analysis in lieu of identity testing. We have reconsidered that and in the draft proposed rule when you use a COA from a rival supplier you don't need to perform an ID test on each component lot or to conduct a visual ID of each lot of containers and closures. Those two provisions have been in the 1999 regs.

[Slide]

Regarding reserve samples, there was opposition to the requirement to keep a reserve sample from each batch for 30 days because sometimes the patient might require an entire batch. We recognize that and agree with that, and the proposed rule deletes the reserve sample

requirement.

[Slide]

Another issue relates to final release of a finished drug product when there is a temporary equipment breakdown. The concern was that release shouldn't be barred if there is an inability to complete a particular test in a certain circumstance. We still haven't resolved what our position is on this, and we are seeking comment on whether to allow such release and what the conditions might be. The draft proposed rule addresses questions and seeks information about the frequency of breakdowns, on the unavailability of alternate test methods, on the possibility that a different PET center might be able to provide a drug to the patient in such circumstances. If we are to permit release, what type of conditions there might be, and should the receiving facility be notified in such circumstances.

[Slide]

Another concern is process validation. There was one written comment that maintained that retrospective repeated end product testing ought to be sufficient at least for certain well-established drugs. We basically concur with that in the draft

proposed rule and we say that if a PET center has a history of producing a particular drug, then retrospective validation is adequate if there hasn't been any change in the process and there haven't been any process related failures.

[Slide]

I will briefly talk about some of the other changes that we made to the 1999 draft regulations. We replaced the concept of theoretical yield in the master production and control record with action limits on radiochemical yield. We clarified that for a drug that is produced in sub-batches that you only need to show that the initial sub-batch that is representative of the entire batch conforms to specification. We agree that, because of the short half-lives of these products, if we required the completion of testing of all sub-batches in a lot of cases there wouldn't be any usable product.

[Slide]

Some other changes, we deleted the requirement to notify the prescribing doctor of a sterility test failure. We agree that notification of the receiving facility is sufficient, and a lot of times the PET center isn't necessarily going to

know who the physician is anyway.

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We deleted the requirement for specifying the contents of the drug product label. We agree that that is not a proper CGMP requirement. The contents of the labeling are going to be addressed in the approval. They are going to specify what goes on the label. So, that will be addressed in that context.

[Slide]

We deleted the requirement to confirm that prescriptions are reviewed to ensure that they have been properly filled. We agree this isn't the responsibility of the PET center. It is basically the practice of pharmacy. And, we have reduced the record retention requirement from three years to just one year.

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So, where do we go from this point? We will, of course, consider all the comments that we receive today. We will consider the written comments that we have already receive and will receive. As Jane mentioned, the comment period runs through June 5th but, of course, we will consider comments we receive after that point as

long as we are working on it. We will make appropriate revisions to the draft proposed rule and issue a proposed rule. We will probably have a 90-day comment period on that. I think Jane has mentioned the possibility of another public meeting, if necessary, to consider the proposed rule. And, we will review any comments we receive on the proposed rule, revise it as appropriate and then issue a final rule which, at this point in time, I think we would like to do sometime in 2003.

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With respect to the draft guidance, depending on what happens today, we might need another public meeting to discuss some issues in the draft guidance, but we will need to revise the draft guidance to reflect any changes that we might make to the draft regulations and, of course, any comments we receive on the draft guidance itself. We will issue a new draft or a revised draft when the proposed rule is published. Of course, we would consider any comments we receive on that revised draft guidance and then issue a final guidance concurrent with the final rule.

I think now we are going to move to a discussion of particular issues of the draft

proposed rule.

AXELRAD: Thank you very much, Brian. Before we get into the specifics, does anybody have any questions on the regulatory process or the different status of the documents, the relationship between the rule and the rule codified, the preamble and the guidance document? I think it is important that people pick up on what Brian said. The regulation itself, which is what we are required to do under the statute, is in two parts. There is the codified, which is actually what are the binding requirements on the PET producers, and then there is the preamble language, which is explanatory material that sort of explains how we got to the regulations and things that we considered in setting the requirements. It is sort of like the legislative history of the rule, like there is a legislative history for a law.

The guidance document is a non-binding document. It is put out because you can't put in the regulations a lot of detail of what kinds of things would be acceptable ways of complying with the regulations. So, we issue guidance documents that are not binding on either the agency or the industry, and we issue them in accordance with our

good guidance practice regulations that tell how we develop them, how we get input on them and what kind of wording we put out. We are very careful not to have any mandatory wording. As Brian said, if you have alternative ways of complying--what we put in the guidance document are some ideas of how we think people could legitimately comply with the regulation, but if people have other ways of doing it or they want to propose alternatives, they are absolutely free to do that. Our inspectors are not permitted, for example, to go out and inspect your facility with the guidance document in their hand and say, oh, you didn't do this; you are in violation. It is the regulation that is the part that is binding. The guidance document is simply explanatory material. Does anybody have any questions about that before we go forward?

PARTICIPANT: Could you give us some idea of the inspectors? Are they going to be local people? [Not at microphone; inaudible].

AXELRAD: I will let you get away with not using the mike this time, but everyone has to use the mike and identify themselves.

Anyway, the question was what about the inspectors? I think that our plan all along in

doing this has been to train a group of FDA inspectors. I mean, they are not going to be special people but there will be a group and I will let Brenda comment on this further, but we will have a group of trained people who will be trained to understand the regs and the guidance, and what we are looking for. Brenda, go ahead.

URATANI: I would also like to say that this regulation becomes final we plan to issue a special inspection guide for FDA investigators so they will know how to inspect a PET center. All the inspection reports, instead of going to the district for review, will come to the Center, to us, for review because we feel that we have the most experience with PET manufacturing or PET production. Also, during the initial period, when this will become finalized, we will also exercise regulatory discretion. So, I don't think you will have to worry about FDA coming to inspect you.

AXELRAD: Go ahead, Dennis.

SWANSON: Dennis Swanson, University of Pittsburgh. I would like some clarification about guidance documents. It has been my experience as part of the regulated community, it would be NRC regulations, FDA regulations, human subject

protection regulations, you name it. Guidance documents and guidance statements actually, in fact, become de factor regulations. They reflect the agency's policies as to what they consider to be acceptable to meet the requirements. I think a lot of people in the community would probably agree with that. You end up getting cited because you are not in compliance with some guidance document statement, or some interpretation of the regulations by the federal agency.

You know, I would really like some clarification of that because I think that is a critical issue that we have in front of us because I don't have a lot of major problems with the regulations but I think the guidance document goes into excessive details, excessive requirements in many areas that are going to be very difficult for some of us to comply with. So, we definitely need a clarification of that before we can go too much further in this process.

AXELRAD: As I said, the guidance document is not binding on FDA or the PET producers, and there is a statement in every guidance document, like a black box warning in a guidance document: this draft guidance document, when finalized, will

represent the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

So, the purpose of this really is to explain what our current thinking is, how we interpret the regulations, and acceptable ways of complying with them. Can I tell you that a hundred percent of the time this is the way it is used and nobody ever views it and cites it? No, I can't control everybody but we certainly try to do that. And, I think we will be very interested in hearing from the community about whether they want more detail or less in the guidance document; where it does go into detail, what they find troubling or difficult; if one were to go and say that the regulation requires a certain thing and the guidance document explains what that means, where that is problematic for the community.

SWANSON: Since it is not binding on the FDA or the community, would you then be amenable to an approach where the community and the FDA would

work jointly to develop a guidance document that would perhaps go into greater detail, where we feel that those areas of greater detail are necessary and would eliminate some of the excessive requirements that are in the current guidance document?

AXELRAD: Well, I think this meeting and all the other meetings we have had is an attempt to do that jointly with the community.

SWANSON: In this meeting and the other meetings that we have had, we have given statements and many times those statements don't appear in the guidance document. I would propose a process that is similar to the USP process where we work very effectively with the FDA to jointly develop the chapter on compounding and expand that chapter. In other words, I think that the PET community would actually like a greater voice in the development of this guidance document because of some of our concerns.

AXELRAD: Well, I think that we have a mechanism for doing that. Unfortunately, the USP process isn't a public process. For the USP you get together in a room with whatever small group of people fit in a room and then you try and hash

things out. I think that the audience in this particular public meeting is indicative of the fact that our audience and the public interest in what we are doing here has grown considerably. Like I said, there used to be about five or ten people who would come to these meetings, other than the people who were at the table. Here, I think there are well over fifty people.

I think that under our good guidance practice regulations we have a process for developing guidance documents that includes extensive public input. This public meeting is a part of that. We believe that we have been very responsive to the concerns and have made changes. The guidance document has never been out there before so, you know, it isn't that people made comments and we weren't responsive. Previously we have only been talking about the regulation. So, we really want to get people's views here at the public meeting today, and in writing, and we will consider them and we will have another public meeting, or as many public meetings as it takes, to make sure that at least people understand where we are coming from.

I think the comments and the opening

remarks today indicate that there is a spectrum of views on what we ought to be doing in the regulation and the guidance document, and I think it is important that our process be an open one that takes into account everybody's views. So, that is sort of what we are proposing to do.

DR. SWANSON: You are in error, the USP process is definitely a public process. There was a working task force that included representatives of the FDA and the regulated community that worked on specific details of each requirement and discussed them at length, and debated them, and came to agreement on them. That produced a working document that was then put in front, with public notice, just like the FDA process. And, there is nothing to say that you can't make this a public process. What I am talking about is actually having a working task force that sits down and discusses and comes to agreement on each point within the guidance document. You can still submit that to a public process, just like what you are doing now.

The problem you have right now is you go back, your people work on a guidance document with no specific input on each point. I suppose we can

do that here if you are willing to take on the task of discussing each point, but I am not sure that that is going to be accomplishable with this large a group.

AXELRAD: Well, I would like to see what we can accomplish today. I think that it would be very difficult for us to develop the document in that kind of a closed setting, and I don't think that we are really allowed to do that under our good guidance regulations.

But I wanted to acknowledge Brenda and Tony who took this over from Tracy Roberts when she left the agency. Brenda has made a large effort to get out into the PET community. She has visited--I don't know how many?

URATANI: More than half a dozen PET centers.

AXELRAD: More than half a dozen PET centers. She has talked to people in the community; she has been out to the facilities. And, I think she has done an incredible job of trying to understand the concern out there in developing the guidance document. The document you have in front of you is our first effort to write down what we learned and how far we have actually

been able to go in terms of addressing the issues. I think in the discussions today we hope to get a lot more information from you, and Brenda is actually going to start now to lead the discussion. We are going to start with the regulation and then go into the guidance document, and see how far we actually can get in discussing the issues.

CONTI: I am sorry, but I just want one more clarification before you start. I suggest you go visit the University of Pittsburgh.

URATANI: Thank you very much for the invitation.

[Laughter]

AXELRAD: I would like to go visit the University of Pittsburgh.

CONTI: The other thing I would comment on is I would like to know at this point, and I know this will come up again later, the definition of a PET drug as appropriate for these regulations, whether these are NDA approved PET radiopharmaceuticals or are they investigational drugs? I need an answer to that because that will set the tone for the rest of the conversations.

AXELRAD: Well, as you can see, we very cleverly put that issue of what the CGMPs will be

for investigational new drugs and research drugs at the end of the day since we figured that if we put it at the beginning of the day we might never get off it.

In terms of the discussion today, I think we ought to look at these in terms of their applicability to approved drugs. I would like to hear, certainly, later on in the day what people's concerns are about applying them in a research or IND context. I think we will probably have to have another whole session to discuss that in more detail, but we have left time on the agenda later in the afternoon to talk about what the problems are with applying something like this to INDs or research drugs.

CONTI: I think that is a very good approach actually. Just from a position point of view, the Society of Nuclear Medicine will take the stance that there will be no agreement on regulations until there is also agreement on IND and RDRC approval processes.

Discussion of Preliminary Draft Proposed Rule

URATANI: I am a relatively new person in the committee and in order for me to have a better understanding of the PET drug production process

and the current practices and operations in different PET centers, as Jane has mentioned, I visited a number of PET centers in the last two years.

Among the PET centers I visited are large and small academic and hospital PET facilities and commercial facilities, which in my mind represent a full spectrum of the current PET production facilities. Actually, I was very pleased to find that most of the facilities are pretty much in substantial compliance with CGMP. I also appreciate the comments and concerns communicated to me during the visits and also after the visits.

All this helped us to prepare the guidance document which, in my mind, I think is more realistic for the PET drug production. Also, we revised our proposed regulation to address the concerns, as Brian has outlined in the introduction, and we published the companion draft guidance to give you examples of how CGMP can be achieved.

Please keep in mind as you go through the guidance that there is a difference between "must" and "should." "Must" refers to the requirements specified in the proposed regulation and "should"

is the recommendation and suggestion for how to achieve those requirements. There are many ways to achieve or satisfy those CGMP requirements.

In the guidance are examples and recommendations based on our experience in other drug manufacturing scenarios. However, we take into account the unique nature of PET drug manufacturing. Certainly, you can use alternative approaches to satisfy those CGMP requirements. I think while you are worried that the inspector will go out and said, well, you did not follow the guidance, I don't think you have to worry about that much because, first of all, they will be trained, and that is a guidance and inspectors do not cite a violation because you do not follow the guidance. At the end, the inspection report will come to us and we will make a determination of whether they are valid or not.

So, today I am looking forward to having an open discussion with you. First, I would like to open the discussion on the preliminary draft proposed rule, and I think foremost in your mind, a topic that you would like to discuss, is the distinction between PET drug production and the practice of pharmacy and medicine.

FDA has determined that CGMP applies all the way up to the finished dosage form, then for the dispensing and administration to the patients it will be under the practice of pharmacy and medicine. Of course, there are many different scenarios for how it is being dispensed. If you have any questions, we would like to hear comments. Dr. Barrio, would you like to make comments on those?

BARRIO: I think the document, from my interpretation and the interpretation of others, is rather unclear as to where the regulations will stop and the practice of medicine or pharmacy will start. I think also in relation to the issues of where the batches are produced versus where the doses are prepared, in some centers, for example--I am referring to academic centers mainly and our hospitals, it may happen that the cyclotron produces the batch and then the dose is prepared in the same site. Then the physician is there or a pharmacist could produce the dose. At the same site means maybe the same room or the room next door. That is what I am trying to say. In some others the cyclotron is very distant from where the scanner is. It may be 100 yards or 200 yards.

Then, big batches can be sent to nuclear medicine clinics where the study is performed, and the dose is prepared locally there, not necessarily at the site of production.

Another confusion is about the non-specific nature of the different situations in the different centers may confuse some people as to where the FDA will stop and where the practice or pharmacy will start, that kind of stuff. I think what is happening is different even for academic PET centers and I think some clarification is needed. I think that is probably the main comment I would like to make.

AXELRAD: We certainly recognize clarification is needed. Pretty much everybody we have heard from at all on this has said that it isn't clear. So, it certainly needs to be clarified.

I was wondering if you had any specific suggestions, I will ask people at the table first and then anyone else, as to how one would draw the line. I think Ravi has a couple of illustrations that he has done that sort of show, sort of characterizing in boxes, the different operations. I think the question is where do you draw that line

in saying that the federal jurisdiction in federal good manufacturing practices stop and the practice of pharmacy or medicine begins. I am going to ask Ravi to take us through his diagrams and then get some input from people about where we think it ought to be, and I would like to hear why you think it ought to be there too. I mean, there ought to be some rationale for where one would draw the line.

KASLIWAL: Good morning.

[Slide]

I have put together a scenario where the way currently a lot of the PET drug production has been manufactured and where the production operation will get transferred to the pharmacy operation.

[Slide]

Basically, PET drug products, the way we see it, just like any other radiopharmaceutical, could be packaged in different configurations. Basically, if you look in USP, general chapter 1 and general notices, there are definitions for these configurations provided in there. So, you could have a pharmacy bulk pack, which is the most common it seems to me, and a single dose container

and a multiple dose container. I know in the community out there the multiple dose container term is used rather loosely, but the USP has a definition. To me, it appears that most of the PET drug products produced would fit into a pharmacy bulk pack scenario.

AXELRAD: Ravi, in terms of PET production, can you explain what you mean by pharmacy bulk pack and why you think that terminology would apply?

KASLIWAL: I will briefly read the definition of pharmacy bulk pack and why I think it fits the pharmacy bulk pack scenario. Basically, a pharmacy bulk pack is a container of sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy, in this case a nuclear pharmacy, as described in USP general chapter 1. The pharmacy bulk pack is exempt from multiple dose container volume limits. So a multiple dose container has a volume limit of 30 ml, but pharmacy bulk pack is exempt from that. The requirement is that they contain a suitable mixture of substances to prevent the growth of microorganisms. My understanding is that most of the PET drug that is produced out

there does not contain these substances to prevent the growth of microorganisms. Hence, they would tent to fall in pharmacy bulk pack category.

KEPPLER: Ravi, but the pharmacy bulk pack would have to go to a pharmacy, not to a clinic in the case of, like, Dr. Barrio's lab?

KASLIWAL: Yes, I was going to describe that next. So you can have different scenarios where basically a production site would release their package to the nuclear pharmacy. It could be within the same building. I am using the term final release, but in the regs we have defined that as long as you have control of the product you can send the product out to the facility while your testing is going on, but there has to be that control factor and we have defined that.

Once it is received in the nuclear pharmacy, the pharmacist will then prepare single doses following pharmacy practice USP or any other producer directions, and then dispense or practice pharmacy or medicine to the clinical site. So, we will not inspect that operation.

It is a different scenario. You could have a nuclear pharmacy in a different building, in a hospital, but basically the scenario remains the

same.

PARTICIPANT: [Not at microphone; inaudible].

KEPPLER: The question is if you are in a clinic you might not have a pharmacist. The technologist might do it under the auspices of practice of medicine.

KASLIWAL: Basically, if the practice of pharmacy and medicine allows that, that is a state regulation so that is how it would go.

ZIGLER: Ravi, on that slide, where does the FDA regulation stop?

KASLIWAL: At the point of final release.

AXELRAD: Show them where.

KASLIWAL: Well, if the production facility is releasing the pharmacy bulk pack to the pharmacy, in the case the nuclear pharmacy would then be the receiving facility. Okay? So, you are releasing it to the nuclear pharmacy.

ZIGLER: So, you can call the nuclear pharmacy the receiving facility?

KASLIWAL: Yes.

ZIGLER: The document doesn't say that though, the definition of receiving facility doesn't include the pharmacy in there.

KASLIWAL: Well, it says for example, but if you so wish, we could include that.

AXELRAD: May I ask you a question? My only concern with that is that if you define receiving facility as a nuclear pharmacy, is it likely that your entire operation is called a nuclear pharmacy, in which case, you know, if we say that the line stops at the receiving facility and you define the entire operation as a nuclear pharmacy, where then do CGMPs begin and end?

ZIGLER: Well, we can split that within one facility. We can have well-defined pharmacy practices in one room and well-defined GMP practices in that same room. So, the entire room wouldn't be a pharmacy.

HUNG: If you classify the entire facility as a nuclear pharmacy, can the state board of pharmacy come in and regulate the portion that you actually designate as manufacturing? I mean, who has the right to regulate that part?

ZIGLER: Well, the state board would.

HUNG: Who are we going to listen to, the state board pharmacy or the FDA for that manufacturing site portion of the nuclear pharmacy?

AXELRAD: Do you think there is going to

be a big conflict where we are coming in and saying the room ought to be clean? Do you think there is going there is going to be a conflict on that? I mean, cite to me one or two things that you think would really be examples of where there would be a conflict between the state and the federal requirement.

HUNG: Since you license the entire facility as a licensed nuclear pharmacy, I believe the state board pharmacy has the right to come in and regulate you, and that includes the portion that you designate as the manufacturing site. If that is the case, then who should we listen to, the FDA or the state board of pharmacy? There are going to be a lot of conflicts there.

ZIGLER: Well, you would have to clarify that with the state board as well. You have to fight them as well.

AXELRAD: Go ahead.

JACKSON: Mark Jackson with GE Medical Systems. We have fought this battle with several labs that I have set up with the state boards. As Steve says, it goes through the individual state but the clarification I think we need is let's say the synthesis box sends the FDG into the sterile

cabinet or dosing hood, or whatever, and we draw the quality control sample, at that point that is where we have perceived that the good manufacturing regulations will stop and dosing will begin, even though it is done in the same facility, in the same room, even in the same hood. Is that something that we could assume we are correct in? Because as Joe and Steve have mentioned, every time Jim Lamb and I have tried to go to the state board and say, hey, we've set up these two rooms as our pharmacy and the manufacturing area is out here in this other area, and we meet all the regulations for the pharmacy as far as square footage and what we have in those two rooms, and everything, we have not been able to get the state boards to sign off on it for the most part. Would you agree with that, Steve? I mean, you have done as many as I have.

ZIGLER: State boards can be troublesome, yes.

JACKSON: Yes. So, it is very hard to designate that this is the manufacturing area and this is the actual pharmacy per se. So, we do need more guidance, I believe, in exactly how we can regulate those two. Thank you.

AXELRAD: Well, if state boards are

troubling we would be happy to regulate the entire facility.

[Laughter]

JACKSON: Touche.

ZIGLER: Jane, one point, let me clarify just for a second, what happens is when you do this all in one room, the most efficient way for it to happen is to some of your final manufacturing steps in the same hot cell. This is what Mark was saying, the same hot cell where you are going to do your pharmacy business. So, that is where the line gets blurred and we just have to be careful. We recognize that we have to do this on a state by state basis with the boards, but we have to be careful in this audience today to make sure that that is okay.

AXELRAD: I think it is clear that we believe that you certainly need to follow CGMPs through the sterile filtration into the vial. That is clearly part of producing the pharmacy bulk pack that Ravi was talking about.

Again, I would like some specific examples of cases in which you think that the state requirements, that the state pharmacy board is going to come in and impose a requirement on you

that is directly in conflict with something that we are doing. I think that the CGMP regulations are very broad and not very specific. So, I have a hard time understanding what kinds of conflicts you are talking about.

We have been talking about this in, like, four or five meetings now where we have had sort of concerns raised. I would like to hear some specific examples of a conflict so that we can take it back and sort of get a better understanding. We can also certainly be talking to the state boards and NABP, the National Association of Boards of Pharmacy, about this problem. But I would like whatever specifics we can get here on this.

CONTI: One example is having a pharmacist on site. You may be doing the manufacturing in the same room and actually have the pharmacist there to do the dispensing in that particular room and, yet, there is no one supervising the licensed radiopharmacy. So, that could be a violation in certain states. Otherwise, you would have to have a pharmacist there present around the clock for any activity that goes on in that facility if you are in this configuration where you are doing everything in the same hood.

AXELRAD: Isn't that a problem more with the state pharmacy defining the facility as part of the practice of pharmacy, the whole facility, rather than anything we would be doing in terms of GMP requirements?

CONTI: That is exactly it but you wanted a tangible example and that is exactly one of them.

AXELRAD: But how does that influence us? I mean, how could we change? We can't change how the state defines a facility. We would just say that we want you to follow GMPs for that facility, keep the ceiling clean, you know, do it under a hood--

CONTI: I am not saying you could solve that issue. I am just saying that that is an example of the conflict. Whether it is a state issue that they need to resolve, that may be the case. Ultimately you may have to physically separate the two in order to get through the system, or practice under medicine or some other process in order to get to the next step. But I am not saying that FDA has to resolve that or should resolve it. It is an issue though.

ZIGLER: May I make another comment on that? It is possible to separate the two

facilities. Even when you do that though you still find yourself in the situation, and this is where you can make a difference, where you are doing some of your final manufacturing steps in the pharmacy. So, ultimately, the inspector is going to want to come into your separated pharmacy area and that is where you can do something.

CHALY: Thomas Chaly, from Northshore University Hospital. Most make the product and the dose in the same room. There is no separate nuclear pharmacy, and when they make the doses we are using the nuclear medicine technologists to make the doses. The pharmacist is not there all the time. So, if it has to be drawn by a pharmacist there are going to be a lot of problems for people like us because in most cases the dose is drawn by a nuclear medicine technologist and nothing has happened so far.

CONTI: I don't think that is what they are saying. They are just trying to define the scheme here. You could practice under medicine and have a technologist draw the dose.

CHALY: That is true.

CONTI: So, that is really not the issue here.

CHALY: But your state determines that.

BARRIO: I agree with the comment, I think it should be clarified that, of course, many PET centers don't have pharmacists, and what do we do in this case? Well, I think the situation is that the square at the top that is defined as pharmacy bulk package I think is the batch that we produce on a larger scale, and that batch that we produce on a larger scale can be transferred to the clinic where the physician will dispense the dose to the patient. I think that could be a situation that may apply to many PET centers without pharmacists.

CONTI: It should also be the same scenario whether it is a nuclear pharmacy receiving it or a physician receiving it. It should be the same scenario, the final release should be the cut-off point.

KASLIWAL: From our point of view, from the inspection point of view, the final release is the cut-off. I am just presenting a scenario here to you, beyond final release how you use it.

FERRIS: I don't know of a nuclear pharmacy law that would prohibit the manufacture of FDG, for example, according to CGMP within the framework of a nuclear pharmacy. I think the issue

goes to whether or not a state board of pharmacy interprets the drug manufacturing process as being within the regulatory authority of FDA rather than their regulatory authority. That is where the conflict happens until you get it to this point because in a significant number of state boards they ask for descriptions of issues involving a cyclotron, which have been talked about here for four years and are relatively resolved I think, but not necessarily resolved with the state board.

AXELRAD: I would like to see if someone could articulate what one would like us to say. I am having a little trouble understanding which way we want to go here. Do you want us to say that federal jurisdiction in GMPs applies up to the point of final release, which would be, you know, sterile filter into the vial, and saying, okay, we have done our testing and it is finished for the sterility test? And, essentially the federal jurisdiction preempts state law up until that point, and then at that point the state comes in and regulates it? Is that what you are asking us to say?

[Several participants answer "yes"].

CHALY: There are many centers now that

are not manufacturing FDG; they are just buying FDG. So, it should end at the filtration and the final vial. There are private companies manufacturing and shipping into the facilities. So, there is no point in putting any restrictions there after that.

FERRIS: As long as the scenario that you present doesn't preclude the opportunity for a PET center that doesn't have a nuclear pharmacist pulling patient-specific doses, that they have the opportunity to take a finished drug, multi-dose vial, and send it up to the clinic whereby, under the practice of medicine, doses can be drawn.

SWANSON: But understand that you still need to comply with your state board of pharmacy requirements. Nothing within these FDA regulations is going to relieve you from complying with whatever your state boards say with regard to dispensing drugs. Now, that can be done under a pharmacists or, in many states, it can be done under the authority of a physician. But you need to go find out what your state boards say with regard to that. You can't label this part of your facility a "pharmacy" and not have a pharmacist there because that is a direct violation of your

state pharmacy laws. Okay?

AXELRAD: I don't think we are trying to affect that at all.

SWANSON: You can't.

AXELRAD: No, we are not trying to in any way affect your relations. I think I have a better understanding now of where people are coming from, actually probably for the first time in all the times we have discussed it. Do you have one more comment?

MATTMULLER: I am Steve Mattmuller, from the Kettering Medical Center, in Kettering, Ohio. I think you are on the right track with stopping at final release. I think what you really need here is someone from NABP because I think the experience that Mark has had, and other people have, is that states board of pharmacy are clueless as to what is going on in this room. They don't understand what a cyclotron is. They don't understand making a PET radiopharmaceutical in the matter of half an hour or so and dispensing it to a patient. So, I think we are having a lot of our troubles with this issue specifically with the individual state boards who need help in education to be brought into this process and, hopefully, in future meetings you will

do that.

AXELRAD: We will certainly do that. We have a good working relationship with NABP on a number of issues, including pharmacy compounding, other parts of it, from the FDA Modernization Act and we will certainly talk to them about that. We have not had a specific discussion with them about PET and we will certainly do that.

SWANSON: Before we are off this topic, it is noted that Part 212.1 of your proposed regulations defining production means the manufacturing, compounding, processing, packaging, etc. There may well be situations in the future where a pharmacist needs to compound a PET drug product to meet the specific needs of an individual patient, and I would hate to see you legislate that ability out of existence by including compounding in this definition. So, it actually gets back to the same compounding issues that you are dealing with under Section 124.

AXELRAD: I don't think it has any connection with 124 because even though they use the word "compounding" in Section 121 on PET, they specifically excluded PET drugs from compounding under 124.

SWANSON: I understand that but your definition of production under this proposed regulation includes the term "compounding."

AXELRAD: Well, that is because the statute used it. It says it applies to the compounding of PET pharmaceuticals.

SWANSON: All I am saying is if it does that, then in the future if there is a need for a PET drug to be compounded to meet the specific needs of a given patient, then that is going to have to be subjected to all of these same requirements under your proposed regulations.

FERRIS: On this same point, the guidance document, line 174, talks about--where we sort of clarify here the ability to dispense under the practice of pharmacy in medicine, the guidance document at that point also includes distribution. Typically, under the practice of pharmacy is dispensing and distribution of patient-specific doses, but the guidance document extends the CGMP to distribution. Are you intending to include as the practice of pharmacy as well?

URATANI: The distribution that we stated in the guidance document refers to commercial distribution.

KASLIWAL: Remember that you can have a single-dose container or a multi-dose vial in addition to pharmacy bulk pack. Besides, the pharmacy bulk pack itself could be in the distribution system, let's say, to a central radiopharmacy.

ZIGLER: But the pharmacy bulk pack may also just be in the same room.

KASLIWAL: It could be, yes. Then, you would have limited distribution.

ZIGLER: it would be very limited, yes. Jane, if I could make one more comment? To me, I think one of the things that needs to be clarified--I think Bob's comment on line 174 is very important. I think line 166, that sentence, hopefully, is poorly written. Also, I think throughout the GMPs there doesn't seem to be--I like Ravi's slide here; I think this is a big step in the right direction, but I don't think it was written with this in mind. The wording in a few places, like when you talk about distribution, when you talk about records, when you talk about patient names and things like that, that would be something through pharmacy you would get that kind of information from the pharmacy element, not from the

manufacturing element.

AXELRAD: We would welcome specific suggestions as to how to rewrite these sentences to make them clear. We can certainly include a chart like Ravi's chart in the guidance document and then try and describe it in text, if that would be helpful.

ZIGLER: I think that would be a good idea, with a big red dotted line between FDA regulation and pharmacy regulation. I think it is also an excellent idea to include NABP. If you do that, we would welcome the opportunity to participate.

BARRIO: I would like to also stress the necessity to make sure everyone understands that those centers not having pharmacies are covered. I think the way this discussion is moving, it seems to define very clearly where the FDA regulations will stop, and I think we call it batch, defining the opportunity for both, the practice of pharmacy and the practice of medicine to proceed from there. It will be very important to make sure that there are no issues in regards to those who don't have pharmacies in their facilities and still comply with the practice of medicine.

Then, my comment is related to the fact that we just include this graph alone in the guidance, I think we will have a set of questions coming from a lot of PET centers not having pharmacists, and then we are going to add to the confusion rather than to clarify and solve the problem.

CONTI: One of the things that could be done to articulate that better would be to have a box that describes an appropriate facility, and maybe give some examples in the text. So, it could be a physician appropriately licensed or facility or a nuclear pharmacy, etc., etc. So, there needs to be a bit more articulation of what the appropriate facilities are in the text, but the box could be more generic.

INNIS: Bob Innis, from NIH. I was going to say exactly that. Would it be easier to just say that the CGMP applies up to the final release, at which point it could be transferred either to a nuclear pharmacy or the control of a physician and, thereby, under the authority of pharmacy or physician control. So, if it is just specified, I think that would be helpful if there are any problems which occurred with state boards, the

orientation of the FDA would be clear.

URATANI: That was our original intent. We might have written it in a confusing way and we will revise it.

WEINBERG: Hi. I am Larry Weinberg. I have a question specifically about the paragraph starting at 174 through 177 concerning distribution. In this meeting there are stakeholders involved in the production as well as in the use of PET tracers. I am not sure that there are many stakeholders involved in the distribution; it is not a very mature industry at this point but potentially it may have its own needs such that it might at some point become a mature industry. Is this typical, that the pure distribution of PET tracers would be subject to CGMP requirements? If it is or isn't, does it make sense that it should be subject to requirements and yet not really subject to inspection?

URATANI: My understanding is that right now the radioactive tracers are under RDRC, and these are research type of drugs. This is a thing that we are going to discuss later one, at the end of the day.

WEINBERG: You are talking about the

distribution? If you have a commercial distribution, that wouldn't necessarily be under ROC.

PARTICIPANT: He is talking about the truck that carries that final release to the nuclear pharmacy, whatever that is.

WEINBERG: If X delivers a drug from Bayer to a hospital that is FedEx required to be under CGMP requirements?

KASLIWAL: I think there are requirements for distribution control, but not necessarily manufacturing requirements. They are not manufacturing anything.

WEINBERG: Right. That is why I don't understand why that should be subject to CGMP requirements if we are talking about a pure distribution of the drug, which is what it seems to be saying under 174 and 175.

AXELRAD: Brenda, what we need to explain is why did we put the statement in here that the distribution--what is meant by the statement that the distribution of PET drug products will be subject to GMPs? What specific distribution activities? In what wan would GMPs apply to that?

WEINBERG: And is there a need for that at

all?

URATANI: Well, CGMP applies to the life of the drug. I cannot give you an answer right now.

WEINBERG: Right. If we were to draw the parallel to the drug that would be distributed by any drug manufacturer, the Bayer drugs might have lifetimes of years and, yet, the pure distribution may not need to be regulated over the lifetime of that drug.

AXELRAD: I think distributer in the sense of a regular pharmaceutical is a term and there are people who actually pick up, for example, commercial products and then distribute them. They relabel them and repackage them in some cases. I think that that concept has sort of crept in here and I think that we need to talk among ourselves and se to what extent we were being driven by that concept of distributer, and whether there is any role for that concept here. For example, in the commercial context where it is shipped all over the country, I think you would want to make sure that there weren't mix-ups and that the right product got where it was going, and that it didn't get delayed in flight for so long that by the time it

got there it was decayed to the point where it didn't give an image. Those kinds of things I think might play a role here, but I think that we hear you that this needs to be clarified, and we will look at that.

WEINBERG: Thank you for your consideration.

HUNG: Under 21 CFR, Part 211 there is the section called distribution records under the current CGMP for finished drug products. So, in a way I agree with the FDA that there should be a distribution record for the PET drug distributions because PET drugs are currently under the CGMP requirements.

CALLAHAN: Ron Callahan, from Mass. General Hospital. I would like to address again the distribution issues because this is something that I think causes us great concern. For example, there are the comments about the distribution process not affecting the drug properties or quality. I could see a validation statement somewhere, in somebody's mind, that says how do you know that the trip in the truck across the highway to your clinic or your customers doesn't adversely affect that? Does that mean that we have to do

testing at both ends of the pipeline, so to speak? So, the implications of distribution CGMP I think are far-reaching. Traditionally, in all other aspects of radiopharmaceuticals and limited knowledge of other pharmaceuticals says that the FDA and CGMP really doesn't get into that process because it should be distribution comes after final release. So, I think we are getting to a consensus point here that the FDA and the CGMPs will end at final release, but the kicker here is the distribution controls. Certainly, you need to know where you send your product and how to get it back should you need to, but beyond that I think we have a possible problem.

BUHAY: Part 211 is finished pharmaceutical regulation. Of course, the most effective comment on this might be from the lawyers, but the Act establishes the application of the CGMP requirement itself, not the regulation but the CGMP requirement to activities. It doesn't address the places or categories of establishments. It just says things like compounding, wherever a drug is compounded, processed, packed or held.

So, in the case of the distribution, wherever a drug is held, it has to be held in a

sensible way, a careful way so that its quality is not affected. If it is held by the carrier, whoever the carrier might be, that, of course, has no bearing on the producer; the carrier is responsible to observe that common sense or even requirement, but programmatically we don't have the resources to address that because we don't find that it develops into a problem. However, as has been pointed out, should there be some sort of lapse in the progress of the shipment whereby, let's just say, it is held for a week, I mean, if the expiration period is an hour, obviously the quality has been affected but it wasn't the producer that caused that to happen; it was the person who held it. So, the drug's quality would be affected and I guess you wouldn't get an image. Right? That might or might not be important in terms of I guess the time sequence. It might be self-correcting or self-regulating in terms of practice, but the quality was affected by the holding.

Part of the process would have to be to establish the distribution concerns that the producer would need to take care of, and then stop there. That would apply just to that business

establishment, the person doing that.

PENDLETON: I just want to point out that this is addressed in the draft regulations in 212.90. So, if you have a concern about whether we should apply any kind of CGMP, we have two paragraphs which affect distribution. So, if you have a concern about those paragraphs in particular, that would definitely be the place to comment, in addition to the draft guidance. But the requirement is set forth there in 212.90.

BARRIO: But I feel that these issues in regard to distribution, from what I understood in your comments, mainly relate to the fact that when the radiopharmaceutical arrives to the place it is still effective. Right? That is really the basic question. This basic question can be addressed very easily with studies of stability of the radiopharmaceutical. The issue is, is FDG for example with 10 curies per micromolar specific activity going to be effective after five hours? Not the decay, but if the chemical integrity of the radiopharmaceutical is maintained. Well, if it isn't a drug or unless we put it in the oven and cook it, we are talking about room temperature, then these kind of studies can be done in the

laboratory to demonstrate if the stability requirements are kept. Therefore, when we do these studies and the stability is understood, then we can qualify the distribution requirements in terms of regulations. As indicated, this is confusing because it gives the impression that it may have more far-reaching effects beyond the large batch as we discussed. I think that would be very helpful.

AXELRAD: I think we will look into that. Again, I would welcome if people have comments on this, address them to the regulations because the regulations themselves have fairly simple requirements in 212.90. So, if you have specific suggestions as to how to word that differently or difficulties with the wording that is there, I would suggest that you address yourself to that.

Let's move on then to other comments on the regulations. What I would like to try and do, can I get a feel for what comments, just general topics on the regulations themselves, as opposed to the guidance? Can people just throw out topics and we can sort of figure whether we want to take a brief break and then pick them up, or what. Go ahead. We can just sort of go off the record to get an idea of what we are going to talk about.

[Off the record discussion]

AXELRAD: I suggest we take a break, and if you have topics on the regulations that you want to discuss, in the break why don't you come and see me and we will try to organize them into some discussion? Thanks.

[Brief recess]

Discussion of PET CGMP Draft Guidance

AXELRAD: I think we will work until probably around 12:15 and then take maybe a 30-minute break for lunch. Are people going out? Do I need to make it a longer break for lunch or can we do it in 30 minutes? The rest of you who didn't bring in sandwiches, maybe you will look hungry and people will share, or something. So, we will go to 12:15 and break for half an hour so people can eat and then we will resume at 12:45.

In terms of the issues that people told me about, what I am proposing is to discuss them in this order, staffing, quality control, quality assurance, sterility and pyrogenicity, process validation, in-process controls, test procedures, software and appeal process. I think I covered pretty much everything that I heard people tell me that they wanted to address.

PARTICIPANT: Did you get facilities down there?

AXELRAD: Why don't we cover staffing and facilities at the same time? In a way, this sort of follows the topics that were on the agenda, and I think I am going to give up trying to distinguish between the regulation and the guidance, otherwise we will just be having the same discussion when we get to the guidance. So, what I propose is to have a discussion--if you have a problem with the specific language in the regulation it would be appropriate if you would try and explain that as opposed to difficulty with the language of the guidance. Then, at the end we can cover any other topics on the guidance that we didn't address in this list. If that is okay with everybody, we will turn to Brenda and we can start with staffing and facilities.

URATANI: I just want to make a few remarks with regard to staffing. Basically, in our guidance as well as in the regulation we said that you should have a sufficient number of personnel, and we also take into account that if you are a small PET center there might be only one or two persons doing both the production and quality

control functions. However, we do recommend that in larger production facilities there may be a need to have an independent unit for quality control so that the decision for whether to release a product can be made independent of production, and also to oversee the entire operation.

I think we will start with staffing first and later on we will go on to facilities. Any comments on staffing?

EMRAN: About the selection of the organization--

AXELRAD: Could you please come to the mike and identify yourself because otherwise the transcriber will have you by name in the transcript?

EMRAN: Ali Emran. This is regarding--

AXELRAD: Where are you from?

EMRAN: RNP. This is regarding the definition of the organizational element that will be assigned the QC responsibility. This is going to be a very hard thing to come up with because it will create some sensitivities within each organization. Also, it will put a burden to assign one person a separate task. We all do the production and quality control at the same time.

But how can we comply with that without creating any kind of over-burden on the staff and the sensitivities that may be created because of that?

URATANI: Are you talking about a situation where you have only two persons?

EMRAN: Yes.

URATANI: I think in such a situation the two persons can both be trained in production as well as quality control so that if one person is doing the production and testing, he or she can review the records and sign off or the second person can do the signing off.

EMRAN: That sounds reasonable.

BARRIO: Brenda, a comment in regards to this. In the document there are several references about small PET centers and large PET centers. Of course, the first question is what is a large PET center. I mean, we understand we have a large number of people versus one or two. That is very easy, but if you are in between you never know whether you are small or large. That is an issue that needs clarification.

The other one is coming from a large PET center, I can see that the intent here is that if there is a large PET center you have to be in a

specific quality control unit, and I don't see the necessity of that really, realistically, because different people are normally doing different things. Just for the sake of making better use of our budget, everyone has the ability to essentially do everything and, therefore, to assign a specific responsibility--I can see that what this will do in academic PET centers is it will increase the burden and will require more personnel. In research operations, it means that we will be having to pay for that mainly from research resources and this may be an obstacle to the necessity of having in large PET centers a quality control unit. Then, at least in our opinion, it would be best to have more flexibility in that particular area.

URATANI: We will take that into account. I think as long as you can demonstrate that you are able to perform the quality control functions in QA well, as well as production, and also that you are not producing a large amount of PET drugs, it will be taken into consideration that you do not need independent quality control.

CONTI: I think a lot of PET centers probably have one person doing most of this. That is the reality of the situation across the country,

particularly in small centers.

AXELRAD: I don't think that is the case anymore, unfortunately.

CONTI: Well, I am not sure if that is true.

AXELRAD: Well, that is a factual question that would be interesting to address.

CONTI: But just even in the case of a situation where you have a single person doing an operation, there may be multiple staff but one person actually doing FDG production. There may be other things going on, but that person actually does both the production and QC before the product is released.

What I would propose is that instead of having the requirement of multiple personnel, because it has been demonstrated to be very safe and we have never had problems specifically with this type of thing from sort of a tenure perspective, that perhaps some of these could be done retrospectively by that same person in terms of reviewing records and things like that, as opposed to having more than one person being involved in the release.

URATANI: I think our guidance document

did address that and we said that if you have only one principal person you can do self-checks.

AXELRAD: But we really do need to get some data. I am not sure how we do that about how many PET centers only have one person doing it.

CONTI: You may have more than one person, but I am saying they may be doing other tasks. If you have a facility with three qualified personnel, two may be working on other issues or may not even be in the facility at that time. Yet, the one person doing production is there. The point is, is there a need to bring in a second person in to do the specific tasks in order to release the product, and I don't think the answer is yes; I think it is no.

AXELRAD: Well, that is the answer. We have said no. It is clear, and we will make sure that it is clear enough, that we explain that when that is the case you can do a self-check. I think we say that explicitly in the guidance document.

Again, I think that the PET industry has changed since we started regulating this. When FDAMA was past, we understood that there were basically 70 PET centers and they were largely small academic operations. Now we know that there

are over 300 PET centers in the country, and many of them are new and more commercial, and have multiple personnel. And, we are trying to write a guidance document that will fit both situations. So, you know, we are not going to change to the sort of lowest common denominator because there may be a few facilities that have problems complying.

So, I think we have to try and figure out--we have our economic staff person, John Lenish is here. John, raise your hand. We are trying to get some information because in the proposed rule we have to have it supported by an economic analysis as to what the economic impact of the regulations would be on the PET community, and we want to try and get a better feel for how many people really are out there that would have problems, and whether there is perhaps a minority, a small number of facilities who have specific problems with specific sets of requirements, and we could look at what the impacts are on those facilities and then see if there is something we can do. But I think it is really important that we try and get data. So, if anyone, in their comments, either wants to talk to John personally about it or provide written data in any of their

comments on the preliminary draft proposed rule that we could use in developing that analysis, I think it would be very helpful.

CHALY: I am Thomas Chaly, from Northshore University Hospital. It is really confusing to us when you say large production centers and small production centers. A facility can produce two curies in one batch, four curies in one batch. Do you mean by the amount produced or the number of syntheses you are getting out? It is not very clear from your wording.

URATANI: Well, at least in my mind, my thinking, my current thinking about the small PET centers is a production facility in which you have very limited personnel, maybe one or two people working at a PET center doing all the production and QC control, and you are producing a very limited amount of a single PET drug, one at a time, very few doses for your own patients' use and not for distribution outside of the facility.

CHALY: It is still not clear. What you are saying is that if I produce two batches of FDG in my center and I use one person to produce that, one after another, we will do the quality control on the first one, and the same person is used for

the production of the second batch. Do you consider that as a large production area or a small production area? I don't understand.

URATANI: Small.

CHALY: So, you can use one person to do that.

URATANI: Well, do you think that person is capable of doing quality production for two batches?

CHALY: Yes.

URATANI: Okay.

KASLIWAL: Brenda, can I clarify here? One thing is that the way you are looking--I am sensing some confusion. The way quality control is written in the document really is the QA function. The quality control, the way you are looking at it is as part of testing, which is in the definition of production. When you read the document, read it from that point of view. It will clarify a number of issues.

The second is, you know, this gentleman pointed out that obviously we will be looking at, given the resources, whether you can complete your given task in a satisfactory manner, in a timely and satisfactory manner. So, both timely and

acceptable manner. If you can't do that, then obviously you need to have more people.

HUNG: Since Larry mentioned the quality control unit, and as I mentioned in my opening remarks, it seems to me from the guidance that the quality control unit should be independent from the production unit. So, it doesn't mean that we have to hire a group of people or maybe one or two doing nothing but performing that quality control function.

KASLIWAL: It is true, you should definitely avoid a conflict of interest between production and QA function.

AXELRAD: I think Ravi is talking sort of in the general context where we are talking about a large commercial facility. I think the guidance recognizes that we can have the same person checking their own work in a small facility with limited production, that we don't expect the traditional complete independence of the QC unit from production in a case where you are not in a large commercial facility.

ZIGLER: Jane, can I make a comment on that, coming from a commercial operation? I think we need to look at a couple of things here. One is

the size. In the preamble it mentions that a small facility would be one or two doses per day or per week. That is exceptionally small in my opinion. That is a very small operation. I can't speak for anyone else in the audience, but there aren't a lot of places that are that small.

AXELRAD: Where do you think we should draw the line? How do you think we should define small?

ZIGLER: I think it depends upon whether you are regulating the number of batches a facility produces or the number of doses a facility produces. It doesn't take any more work to produce one batch of a multi-dose vial. Correct me if I am using the wrong terminology, Ravi, but it doesn't take any more work to make a one millicurie batch or a one curie batch. So, the complexity of it is basically the same. It is just how long you are going to leave the cyclotron on for.

HUNG: If I can follow-up on your comments, in the quality control section you are actually talking about a small PET center, one or two persons doing the production. You have to invite outside consultants or independent people to come in an audit your quality control performance.

I am saying that if you already have self-check built in, second check, it is really not necessary to have an independent quality control unit to do that.

URATANI: Those are independent outside consultants, their recommendations. I mean, if you can do it other ways, you are welcome to use other ways to achieve the same purpose.

HUNG: I am saying if you already have a second check system built in there is really no need to have another person or group to come in and audit your performance. It is just unnecessary.

ZIGLER: Can I make a comment on that, Brenda?

URATANI: Yes, sure.

ZIGLER: I think it is important also to differentiate, and I think this gets at what Ravi was saying a second ago in terms of the difference between quality control and quality assurance, it is important to differentiate between the execution of quality control procedures and the oversight of quality control procedures. Typically, the oversight is a quality assurance function. That function should reside outside. That should be an independent role, that outside oversight. That can

either come, in a corporate environment such as mine, from a corporate QA. It could be a consultant like what Joe was saying. But in terms of the execution of those quality control procedures, regardless of the size of the facility, we have to be able to do that with one person.

You know, the execution of those quality control procedures, we have to be able to do that with one person who also does the production. And, it doesn't matter whether it is a large commercial facility or a small non-for-profit facility because there are commercial facilities out there that may only produce a handful of doses a day from a single batch.

So, I think the thing to consider here is how you define size, and I think you need to consider batches. I think you also need to maybe clearly differentiate between the execution of quality control functions and the oversight of quality control functions.

URATANI: We hear you.

MATTMULLER: I have a question and a comment. One suggestion for the audience, it is probably not a good idea to come up here on the public record and call your state board of pharmacy

clueless.

[Laughter]

For the FDA, to comment on something that Dennis Swanson touched on earlier as far as what the regulations say versus what the guidance document says, I was real happy to see that in the regulations is says that for small PET centers, such as ours that Kettering has, 1.5 FTEs doing everything, one person can do production and quality. But then in the guidance it says if you are small like that you ought to send it out to an independent auditing firm which, frankly, we can't afford. So, I would also ask if you could write down the name and address of your economic analysis individual because, clearly, we would have comments for him.

But my concern would be that the regulations say I can do it all, but then my fear is the inspector comes in and says the guidance says you ought to have some independent firm auditing this on a regular basis, which I can't afford to do, and I don't know how I could convince him that my alternative means is okay.

URATANI: Well, you can be assured that our inspectors will be trained not to follow every

word of the guidance because the guidance is recommendations. We think it might be nice to have somebody outside take a fresh look but if you cannot afford it and you can demonstrate that you will be able to fulfill the same overseeing function, then you don't need an outside consultant.

MATTMULLER: I guess it has come to the point where if you can't afford it you shouldn't be in the business. To be more clear, I guess I should say we have an established record of doing it in a proper and safe way.

URATANI: And if you see that you don't have a need for it, then you don't need it.

INNIS: I know that the question at hand here is determining what large and small is. If it is large and small, then you would have varying amounts of staffing requirements. My suggestion would be that maybe you should make the staffing requirements based upon the staff available.

Let me explain, given the difficulties of trying to define how many batches or how many doses you can get one from one batch, I don't think that it is really going to be possible or really even useful to try to use a definition there in terms of

productivity of number of radiopharmaceuticals or millicuries of radiopharmaceuticals produced. Instead, the idea of having separate QA and synthesis really applies in a situation when you have many staff and you have staff available to be able to do it, and could those multiple staff be confusing each other or providing conflict of interest in having that done? So, really it seems that having separate staff and separate utility is based upon how many people are working there. I suggest that if you have something, I don't know but for argument's sake, ten to start off with, if you have more than ten staff in the production then you should have a separate QC and production. In that way, it is not the total number of production but the total number of people who are there who would determine that separation.

BARRIO: The question is always the same. Why would you need to have, after you have ten people, a separate unit? And, is that going to ensure a better performance in the center? I mean, you may have ten people because you have 15, 20 preparations a day and maybe those different people may be doing different things, and that is the way you organize your things. For example, in the

preparation of FDG not necessarily would everybody be involved. Practically, when you are in the process of applying CGMPs perhaps a small PET center and a large PET center may be in the same situation because you may have ten people, but eight or seven of them may be doing something else. That is always the question.

INNIS: I hear your point and it seems very valid. So, basically, I guess I probably agree. If you looked at an extreme situation I think you would agree that if you had a thousand radiochemists in a PET center, at some point you would have to separate out the QC from the QA. So, in the extreme situation my argument would work. In the other extreme, if you had only one person, then it becomes clear that you would not have to do that. So, if you had some liberal way of doing that--my suggestion was that it would help to address small PET centers which only have one, two or three FTEs because it would be very clear that they don't have to. If I increased it to fifty, you might be happy but I still hear your point that it would have an arbitrariness to it and may not enhance safety necessarily.

CALLAHAN: Ron Callahan, Mass. General

Hospital. Just one other comment on the definitions or the parameters that define a small versus large facility. I think the number of products, as you say, large number of PET drugs being produced is also irrelevant because, first of all, it is very unlikely that any of these other compounds, other than let's say FDG at this moment for the sake of argument, would be covered under the NDA GMP process. If there was a large variety of drugs being produced, 99.99 percent of them are done under research, which we haven't discussed yet and how that applies, so in fact, probably for my lifetime, there is one drug that will be produced under NDA CGMPs and distributed commercially, and that is FDG. So, if you employ the multiple drug product argument, then everybody might be a huge, large facility but these drugs are done sporadically, under different controls, under different regulations. So, that arbitrarily would put probably every university into the large category regardless of what they do. So, I think that is also a point to consider.

COOPER: Steve, could I follow your cue about execution and oversight? Would you envision that the way the guidance is written now it would

allow for you to appropriately describe your staffing, and would you need one specifically identified person to serve as a QC unit? Could you describe this in your procedures, to have the QC unit a function that might be served on one day or another by different people, provided they are qualified in their job?

ZIGLER: Let me make sure I understood your question correctly first. I thought you were addressing Steve Mattmuller for a second there. I think it is important that on any given day, even for a large commercial operation, patient doses may dictate the production of a single batch and a few doses. So, in that situation we need to be able to do the entire production and the quality control cycle with one person. Does that answer your question?

COOPER: No, my scenario is this is a large commercial center and you have three more people on the staff. Is the QC unit one specific person, or could that be a role that is filled by different qualified individuals?

ZIGLER: Well, this gets to the question that was coming up a few seconds ago, at some point it does make sense to have different people do it,

but to have that become codified I think it really needs to be done more from a work flow scenario rather than codifying it up front where it says it has to be separate.

AXELRAD: The question is whether there is a need for it at all. I mean, the theory is that for things that are really critical and important steps in the process, this is sort of a theme that flows through this whole thing, like making sure that you don't get mixed up when you compound or that you make sure that you set up your synthesis box with the right ingredients in it; that you have checked to make sure that the room is adequately clean and sterile, for the things that are critical for ensuring the safety of the patient, the question is, is it better to have one person do it and another person check it, or is it okay to just say, well, we would rather do it with one because it is cheaper to do it with one and, therefore, we should be allowed to do it with one. I mean, nobody here is discussing what the merits are, and there are many merits obviously built in across the industry in other situations for having critical steps be checked by a second person.

We are willing to give some allowances for

small facilities because we have been asked to do that, and to allow self-checks, but I think that there should be some recognition that there is validity to the theory that it is better to have an independent person who isn't going to just say, oh well, I just did that step so obviously it must have been done fine, and sort of gloss over it and not catch a mistake. That is sort of the thinking behind the whole idea.

ZIGLER: Certainly execution of the elements of QC are important. There is no doubt about that for controlling the safety of the product. There is no doubt.

AXELRAD: But I heard you say when we only have one we should only have to have one because that is all we have.

ZIGLER: No, that should be dictated by the complexity of the operation.

CONTI: And also by the track record because, again, we go back to the issue of the tenure of the whole history of this technology, which is that we haven't had the need to have independent quality control procedures. We have been able to do this over the years, in many cases, with a single person in a safe environment. So,

from the patient safety point of view, there hasn't been demonstrable evidence that there is a need for an additional person to do this.

So, what I suggested earlier is that if you want to compromise we could potentially do this either in a retrospective fashion, or you could do it with a quality assurance team. If there are multiple people there you could do performance checks of the individual components of the whole process. In many hospitals they have quality assurance programs where they look at focal areas of investigation. They follow that for a period of time and then they drop it and look at something else and you meet thresholds. You could set all kinds of parameters up, keeping in mind that the history is that there is not a need for this.

Now, if you can tell me that there is evidence that there is a need, I will put it back into your position and I will be willing to listen to that. But from our perspective, I haven't heard of a need for it yet.

AXELRAD: What would I have to show to have a need? Dead bodies? Would I have to have dead bodies to have a need? I mean, these are not approved drugs. There is no adverse event

reporting. How would you know if there had been a problem, other than somebody dying? And, how would you necessarily even attribute it to the PET scan?

CONTI: Other than the traditional ways of finding out?

AXELRAD: Well, the traditional ways we find out is through adverse event reporting and people report adverse events. Sometimes they might report adverse events short of a death. It is difficult in terms of adverse event reporting to even attribute any adverse event to the actual drug. I mean, you have sick people; they are having a lot of diagnostic tests. It would be, you know, unlikely that somebody would even necessarily connect it to that, especially in what is basically a completely unregulated system.

So, I am just saying, you know, we are not going to be able to show you that people are dying in the streets from this. On the other hand, you can't demonstrate that things are perfectly safe either. So, I think that somehow we have to come to some agreement on what are reasonable controls to assure the quality of these drug products, particularly as the industry grows way beyond what it started out as, sort of small research uses in

hospitals, to what is basically a much more standardized diagnostic procedure that many patients are getting and is actually being commercialized.

CONTI: Again, I will go back to the point that you keep forgetting, that we do test every single batch. We have said this over, and over, and over again.

AXELRAD: But you don't get the results until two weeks after the patient has been injected, sterility test.

BROWNLEE: I am January Brownlee, with SYNCOR. I guess my point is that I don't know that it should be dependent on the size, large or small. I think the goal of all quality control activities and quality assurance is the same, and that is to ensure objectivity and to ensure that whoever is making that release decision has clearly been granted the authority to stop shipment, to not release it. So, it would seem that we would want the regulation to talk in terms of what is the actual outcome we are looking for, rather than base it on some arbitrary determination of small, with one or two people, versus large, which might be three or four. That is what I think the reality

is.

So, maybe we should have the actual regulation say must be able to demonstrate objectivity and clearly be able to show evidence that they have been granted the authority to withhold shipment.

HUNG: January, rather than hiring independent quality control people to audit your performance, can we just designate that to the FDA inspector, just like NRC? We don't hire independent consultants to check our record for how we utilized the radioactive material. They have an inspector come to our facility to check every now and then. That is how they confirm the use of radioactive drugs.

CROFT: I am Barbara Croft from NCI. Actually, some centers do hire independent physicists, but they are the little, tiny people and if you don't have a physicist in-house, state regs. and NRC regs. require that you have a physicist for your nuclear medicine laboratory. That person can check this stuff too as long as they know what they are looking for. I am not a radiopharmacist but I have been trained in radiopharmacy as well as in physics and always

check every record--check, check on all sides, not only was it dispensed, but what did the QC look like. So, it is possible to get people. But we are not talking about every day, every hour, every FDG dose. And, that is what the thing says, it says "can get people to come in at intervals." Periodically is not every hour. Periodically is once every three months; once every six months; once a year, something like that.

CONTI: That is fine, Barbara, but I think we are crossing over into release of the product. If you have a single person responsible for releasing that product, production and release and doing the QC tests I think that is still a viable pathway. The question is, and I think we are in agreement, whether it would be reasonable to have this retrospectively reviewed or periodically reviewed. I don't think people would have too much of a problem with that provided that it wasn't overly burdensome.

URATANI: Wasn't this stated very clearly in the guidance document, that one person can do both functions as long as you can demonstrate that you are able to consistently produced a quality PET drug in a timely manner? I mean, that is basically

what we say in agreement to what you are saying.

AXELRAD: I think we have gotten a lot of ideas. I want to hear what you have to say. We were sort of making the distinction of large versus small. I think there have been a lot of different thoughts expressed about other ways that one could do that and certainly the need to make clear whether we are talking about--I don't want to get things confused--quality control of the execution of procedures versus quality assurance of the overall operation and I think we need to go back and look at that.

MOSLEY: Good morning. David Mosley, Eli Lilly. We could certainly agree that the decision as to who does the quality control should be based almost exclusively on merit. What we find as we commission PET studies around the globe is that generally it is the chief radiochemist who is best qualified to both produce the radiochemical and to do the quality control, and for the sake of subject safety, we would like that one person to do both.

Secondly, unfortunately, I am not sure that I can disclose the actual numbers but I can assure you that the economic impact of our audit procedures at these PET centers is quite

substantial, and is beyond what would have been within my reach when I was at the University of Pennsylvania. That is, we are paying something quite significant and the services are not being performed by physicists but by people with doctoral degrees in radiochemistry, in radiopharmacy and nuclear medicine. I hope there will be some opportunity to discuss the economic impact later on in this forum.

AXELRAD: How many facilities do they do QA for? I mean, are you talking about the combined cost of having a group that goes around to a bunch of different facilities? How many do they look at.

MOSLEY: I am not sure I understand the nature of your question, but Eli Lilly's standard is to do quality assurance of every PET center that we work with.

AXELRAD: So, that is a lot.

MOSLEY: Currently, that is about thirty.

ZIGLER: David, what is the nature of your audits? Could you describe that a little bit? Is it clinically oriented or is it CMC oriented?

MOSLEY: We are introducing good manufacturing practices. That is the fly in the ointment, and we have at least two doctoral level

outside consultants that accompany about four to six specialists from within Eli Lilly but, of course, we don't stop there. We also do GCP, which historically has been the main focus of our audits, and, when appropriate, GLP.

WALTZ: Hi. Deborah Waltz, from the University of Pennsylvania. It is great that Eli Lilly does that, but I think in terms of putting standards in place. I am glad that you do that; that is great, but it doesn't meet the needs for [inaudible].

CHALY: Thomas Chaly, from Northshore. I think when you think about one person producing this, there is a possibility to do that. People will worry that that one person can do multiple syntheses at the same time. That should not be allowed. But one person should be able to produce a batch of FDG and he will be able to finish all the quality control and he will be able to certify that before he can release that. That is the way it was done before. But he should not be allowed to do multiple syntheses at the same time because that will be confusing and he can create problems. So, the guidelines should be based on that rather than the amount of FDG produced in the center.

URATANI: Shall we move to facilities, if there are no more comments on this, before the lunch break? With regard to facilities, in our regulation and guidance we said that facilities should be of a suitable design and should have adequate space to prevent mix-up and cross-contaminations. Any comments?

INNIS: Bob Innis again. Some of the earlier comments about whether there is really a problem with the existing facilities, maybe there are no serious problems with the existing facilities and maybe they don't need to be fixed. Maybe we are trying to fix something that is already working okay. But, I have some specific questions with regard to the facilities because the cost of the renovation of facilities will be one of the major, major barriers for PET centers which try to come in compliance with these guidelines.

Being involved currently with the design of a CGMP facility, there are many aspects of it that are very costly but one that comes up is the amount of air required to actually service the area. In this regard, I just want to make sure I have read the regulations and the guidance correctly. To my knowledge, there is no

specification of the air quality in the regulations, but the guidelines specifies only one air quality, and that is that the final filtration needs to be done in a Class 100 environment. Am I correct in understanding that there is no specific requirement then, outside the laminar flow hood, for the air class in the laboratory or in the hot cell?

URATANI: Your question is in two parts. For the first part I want to clarify the statement you said with regard to sterile filtration. If it is done in a closed system, it does not need to be done under Class 100 environment. With regard to the surrounding area, surrounding processing area, for example, in the PET centers that I visited, both of them just have a laminar flow hood. Of course, there are some which are state-of-the-art barrier isolator, but if you have a laminar flow hood there is no specific requirement for the surrounding area provided that is clean and is not going to compromise the laminar flow hood air cleanliness.

INNIS: Thanks. The final filtration--when you say in a closed system, it could be in a syringe?

URATANI: No, my understanding from looking at, say, the FDG, final filtration is that you first assemble your sterile filtration with a sterile vial with stoppers and then you put your syringe and your filters there. That assembly should be done under the laminar flow hood in the Class 100 environment. That is considered a closed system. So, when you bring it to the black box to collect your final FDG, we have no specific requirement for air cleanliness.

INNIS: Well, I think complying with that would be relatively easy. Could I just clarify that you can get a Class 100 laminar flow hood in general laboratory air?

URATANI: Pardon me? What did you say?

INNIS: You don't have to have pre-cleaned air outside of the laminar flow hood in order for the laminar flow hood to be Class 100. So, that makes it much easier to accomplish.

As we are talking about open versus closed systems, there is no specific requirement that the synthesis has to be done, like for novel radiopharmaceuticals, in a closed system. It can be done in an open system. Correct?

URATANI: Well, it will be dealt with on a

case by case basis. I mean, my limited knowledge with PET manufacturing--I mean, I know quite a bit about FDG production, but if you are talking about other open synthesis, we will have to look at individual cases and determine from there.

BARRIO: The question about how you define a closed system, if you define a closed system as an automatic system which is inside a box, that is one way of looking at this. The other way, I think the most appropriate way for making it more flexible, is that the system may be semiautomatic. Automation doesn't necessarily mean better. Automation simply means better radiation protection but the system, with regard to synthesis, is equally or even better sometimes because you have to interact with the system. But the system that you can see when you operate it may be still closed. Closed means that you can transfer liquid, or whatever, in a sealed environment.

The question that I don't know how to address is if you have open parts in that system when you are transferring. You can transfer and have an open system, of course, but that is a differential.

KASLIWAL: I would just like to point out

that from our point of view, from a microbiologic point of view, a closed system would be where the fluid path is closed.

ZIGLER: Brenda, I have a question. You mentioned that the area outside the laminar flow hood needed to be clean.

URATANI: Yes.

ZIGLER: But you are not placing specific air quality requirements on it?

URATANI: That is right.

ZIGLER: Okay, thank you.

JACKSON: To follow-up on Steve's question, that will not keep you from having to monitor the air quality in some way, shape or form to prove that the air within the laminar flow system is clean or sterile.

URATANI: Well, we have no specific requirement about the monitoring of the surrounding area. Is that what you are asking?

JACKSON: You would still have to show monitoring of the laminar flow hood environment though to show that the outside air did not contaminate the laminar flow environment. Correct?

URATANI: That is true, but we are flexible in such a way that are not requiring you

to do the monitoring every day.

JACKSON: Right.

URATANI: So, it is periodically, consistent with the USP. The thing is that right now, it is our understanding that the current manufacturing of FDG is in a closed system so we think maybe the risk is minimum. So, as long as you can show periodically with the monitoring that you are achieving the air quality, as well as microbial limits, that will be acceptable.

JACKSON: My question is a procedural one, as well as a question as to at which point we have to assemble the final sterile product vial. If we are delivering from the FDG box into a sterile laminar flow hood, in other words, the pathway is closed, it goes into a shielded laminar flow hood or similar sterile environment, do we have to pre-assemble a vial or are we allowed to do everything there since we are in a sterile environment post-synthesis?

KASLIWAL: If you are doing the whole thing inside the sterile environment, you can do the whole thing. You don't have to re-assemble.

JACKSON: That allows us to not have the radiopharmacist come into the facility until a

later time in the day, and I just want to make sure that is on the record.

This is another question that many people ask me, I don't know whether it is in the confines of the FDA but if there is anyone who can clarify this, is 100 percent outside air required within the manufacturing and cyclotron facility rooms per se, or is it not? Can anyone answer that question as far as facility controls?

KASLIWAL: In the cyclotron room?

JACKSON: Yes.

KASLIWAL: There is no specific requirement. Should we have one? That is my question.

JACKSON: It would end a lot of arguments with a lot of mechanical engineers if we could clarify whether or not the radiation area, be it the quality control area, the manufacturing area and the cyclotron room, whether 100 percent air is something that is a requirement or not, or if the FDA can give us any guidance on that, because the NRC has as vague a statement as what you just made.

ZIGLER: Are you talking about 100 percent outside air coming into the facility as opposed to recirculating within the facility?

JACKSON: Right. I mean, it has been a constant battle with the mechanical engineers and facilities people. The radioactive areas, be it a cyclotron room or be it the QC area, or manufacturing area, the air handler should be a separate air handler and should have 100 percent outside air being brought in for those facilities into those three particular rooms, or is it allowed to have recirculation within the cyclotron room? Which way is correct? Is there a correct way?

KASLIWAL: We are concerned with the air quality, if it poses a contamination issue to the product. To me, it seems like currently the way are configured it is unlikely. So, your concern seems more like a radiation issue.

JACKSON: It is more a radiation issue, yes.

LAR: Yale and NCI. I wanted to follow-up on Bob's and Steve's question of open system versus closed system. Is it my correct understanding that as far as you assemble your final product vial under a Class 100 hood, you can have any kind of synthesis module or system, open vessel versus closed vessel, and it does not matter as long as we deliver that product through a 0.2 micron filter

into a pre-closed vial which was assembled in a sterile environment?

URATANI: That is right, because when you do the final filtration, I mean the sterility is achieved through the filter.

LAR: Correct.

KASLIWAL: Let me clarify, what do you mean by open system?

LAR: Well, FDG, in my understanding, is an open synthesis unit.

ZIGLER: No. What Ravi is getting at is the closed system is from downstream of the filter, not upstream of the filter.

LAR: Correct.

ZIGLER: So, upstream of the filter an open system is okay, but from downstream of the filter, as Brenda was saying, a closed system is necessary.

URATANI: We are talking about the filtration part. That part is closed. We are not talking about prior to the filtration.

KASLIWAL: Steve, you are correct in part. Closed system is where your vessels, your columns and all that is closed. That is why I asked what is an open system. I mean, do you have beakers

sitting on the hot plate, or what?

JACKSON: Well, the reaction is done in an open vessel and then it goes to a closed system.

KASLIWAL: Open vessel but after it gets closed, right?

JACKSON: Once the product passes through a resin column and passes through a 0.2 micron filter.

URATANI: That is right. That is the current understanding.

HUNG: I have a question about the laminar flow hood or the isolator. On page 12, under section (b), aseptic work station, it seems to me that the agency only focused on the verification of the particulate matter and not so much to the microbial contamination certification. Am I correct to say that in terms of the certification of the hood you don't need to worry about microbial contamination check?

URATANI: Well, the current situation is that we are dealing with a closed system, and there should be certain aseptic practices exercised daily. For example, when you go into you laminar flow hood, every day you should wipe it down and anything that you bring into the laminar flow hood

you should wipe down too, and you should make sure that your laminar flow hood will not be so cluttered that it is going to obstruct laminar flow. Periodically you do the monitoring for the microbial, like active air sampling, and that is all we are requiring right now.

HUNG: Under section (b) there is no mention of microbial contamination check. It is all focused on the particulate matter, the particle count but there is nothing said about microbial contamination control.

URATANI: We will definitely look at that.

INNIS: Let me ask another question specifically about the FDG synthesis box. I have heard from some people who are claimed to be expert on this that the two common commercially available FDG synthesis boxes would not be able to meet CGMP requirements. I am not asking you to endorse either one or endorse any particular product, but is there any reason, from the knowledge that you have about the performance of those boxes to date, to think that they would be excluded from fulfilling the CGMP requirements?

URATANI: In which regard to you think they are not complying?

INNIS: In any regard. I mean, is there any reason to think we are going to have to revise all the FDG boxes in order to come into compliance? Is that true?

KASLIWAL: I don't know what the question would be here.

INNIS: The question would be with the currently available FDG synthesis boxes, do you expect any changes to have to be made to them physically in order to come into compliance with the CGMP guidelines?

KASLIWAL: I mean, I guess we will have to look at the box.

ZIGLER: Bob, correct me if I am wrong, but I think this comes from the fact that some suppliers of boxes claim the boxes to be CGMP compliant. Is that what you are saying?

INNIS: My question is are the PET departments going to have to buy all new boxes or are the current ones okay.

URATANI: We consider the black box as a piece of equipment, and you are using this piece of equipment to do your production run. So, essentially, if you have a new black box you have to do certain qualification, and the qualification

will include insulation qualification, operational qualification and performance qualification. If you have an old box then, of course, you don't need to do the insulation qualification. With the operator qualification you will have to make sure you can operate correctly to establish limits and specifications. That means that you probably will have to identify the critical parameters and check the upper and lower limit to make sure that your equipment will function within that range, and that with the performance qualification there is documented verification that your equipment will be able to operate and that the production parameters will produce results that will meet the established qualifications. So, this is considered as a piece of equipment so I don't exactly know what you meant by the black box that currently in the PET center is not GMP compliant.

KASLIWAL: Let me take a shot at what I think might be the issue. I think in part it might have to do with the in-process controls that some of the boxes may or may not have. Really, your in-process controls are defined in your applications, and if you are able to meet those in-process controls that equipment should be

acceptable as part of the approved application.

HUNG: Ravi, I think the other possible consideration is that in the document is required the so-called time stamp of the system to be built into the record keeping system. So, I don't think that any black box, so-called black box has that kind of capability to do that kind of function. So, if this is going to be a requirement I think there is going to be a major problem there.

URATANI: With regard to the compliance with Part 11, we will exercise regulatory discretion. We understand that it will take time for the PET center to come into compliance with regard to this. However, we do expect that when new technology, new equipment and new programs become available that the PET centers should pursue that and buy those new programs so that they will comply.

SWANSON: Before we leave it, certain specific comments regarding facility sections of the guidelines document, again, I think this points out problems with going into excessive detail. Statements such as the lead-based radiation shielding should be properly covered to prevent lead contamination of the product, I understand the

need for that. If you want to discuss these in greater detail, we can.

There is another statement, phases of production with the potential for microbiological contamination should be performed under appropriate environmental conditions to prevent the possibility of such contamination. In reality, all phases of the production have the potential for microbiological contamination. So that, in fact, creates confusion as to what you want done under a laminar flow hood and what you don't want done under a laminar flow hood, and that is where some of this discussion is evolving from.

You have in here that the aseptic work area should be suitable for the preparation of a sterile PET drug product. In fact, we don't prepare PET drug products in an aseptic work area in most facilities. Rather, we prepare the final container closure system in an aseptic work area. So, again, that statement leads to confusion and it could be easily misinterpreted by anybody who came along and looked at my PET facility.

You have in here examples of activities that need be done in laminar flow area include storage and sterility samples.

URATANI: I think that one will be taken out.

SWANSON: I am worried about the other ones too, Brenda. Container assembly should be prepared at the beginning of the day before other daily activities begin, and before additional personnel have entered the room. That is an excessive requirement. You can easily say that preparation of materials in the laminar flow hood need to be done separate from traffic flow. But these are all examples of where your guidance document is very faulted with excessive requirements.

URATANI: Well, you know, I have to correct one thing that you just said. You said that it is a requirement that you should do it at the beginning of the day. It is not a requirement; it is a recommendation. You can do it in any other ways you want. If you feel that you can do it as the cyclotron is running, that will be okay too. That is the reason why in the guidance document we have "should" and "must." "Should" is a recommendation only. It doesn't mean that you have to do it that way.

SWANSON: Well, this is supposed to be

effective guidance for the commercial and I would like it to be effective guidance for the commercial. Okay?

URATANI: However, you also want not to have FDA to be too prescriptive. So, we just give examples and recommendations based on our experience. But there are other ways to accomplish the same goal.

ZIGLER: While we are on that, Brenda, on line 413 you state that the surfaces of walls, floors and ceilings in the aseptic work areas should be easily sanitized. Is that aseptic work area defined as the room or the laminar flow hood itself?

URATANI: Do you mean 413? The surface of the walls and floors?

ZIGLER: Yes.

URATANI: We don't mean sanitized; we meant cleaned.

ZIGLER: Okay, but the aseptic work area would be defined as the room where the laminar flow hood is?

URATANI: Yes.

KASLIWAL: Yes, if you go to the beginning, the first paragraph of that section, it

describes the aseptic work station.

ZIGLER: So, "sanitized" should be changed to "easily cleaned" then?

URATANI: Right.

ZIGLER: Thank you.

CHALY: I am Thomas Chaly, from Northshore. I do not understand why they wrote that synthesizer thing. Many people are using different synthesizers. Some people are using semi-automated synthesizers. I think it should be based on the validation of the FDG that is produced by the machine that is used, not based on a brand name or that some people say that this box is no good or that box is no good. But I don't know why this black box came into the picture. It was never restricted by FDA. I don't know why.

CONTI: Just to move away from sterility and back to quality control units, I happened to bring a 1994 version of the draft guidance for PET manufacturing. I suggest you take a look at those two sections in there. They are actually very concise and deal with some of the language in the sections very appropriately for some of the discussion that we have had for both staffing and for quality control units.

URATANI: Is that an FDA document?

KASLIWAL: Right, the guidance doesn't exist on paper. It was revoked.

CONTI: I have a copy if you need it.

[Laughter]

LOVE: Excuse me, I think I am getting a signal that we are ready to break.

Whereupon, at 12:14 p.m., the proceedings were recessed, to resume at 12:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

LEEDHAM: Have we finished our discussion on facilities and equipment?

SWANSON: I don't believe that we have discussed equipment, have we?

LEEDHAM: Okay, let's discuss equipment.

URATANI: With the equipment, basically we are talking about qualification of the equipment, maintenance and documentation. Any comments?

ZIGLER: Brenda, I have one comment. In the guidance, in the section on the gas chromatograph, I know this is a give and take where there is even more detailed required or less detail required, I know you are faced with that, but I think it would be nice to have more detail on the gas chromatograph portion because some of the details in the chromatography chapter of the USP are pretty heavy for us. I would just like to offer to take a look at that and maybe come up with some details. I would be willing to, in our written comments, offer something along those lines.

URATANI: Okay.

CROFT: This kind of crosses over into process validation but since it is related to the

equipment, is this a good time for that or did you want to deal with that separately?

URATANI: We will discuss process validation later, but basically this is more for qualification of equipment.

CROFT: Okay, I will come back.

CALLAHAN: Ron Callahan, Mass. General. During the earlier discussion about which boxes might GMPs or something, you were referring to a lot of language that I wasn't familiar with on qualification of equipment. I think in discussing this, a lot of this comes out of 210 and 211 type of qualifications for equipment. Could you speak to us a little bit about that? Suppose we brought in a new piece of equipment like a synthesizer and all these IQs, OQs and other Qs that you were discussing, could you tell us what that means?

URATANI: Suppose you bought a new piece of synthesizer, first of all you need to do your installation qualification. Installation qualification in short is IQ. It means that you should document the verification that this piece of equipment has been installed properly to the established specifications. Normally, the specifications will be defined by the vendor who

makes that equipment.

After the installation, the second stage is the OQ, which is the operational qualification, and that will have to do with verification that the piece of the equipment that you have operates within the parameters and the limits. So, for the synthesizer you will have to define some of the critical parameters. It could be temperature; it could be pressure. There will be certain limits, like upper and lower limit, in operational qualification. We expect that you will challenge the system to make sure that it will operate within the upper and lower limits. Operational qualification only needs to be done initially and periodically. You don't need to do it every day when you use the equipment.

As far as performance qualification, PQ, it is to verify that when you use this piece of equipment it operates under the actual production parameters to produce results which will meet the specifications. So, it is a process.

CALLAHAN: So, where in this document is all this spelled out for us? Or, are we being referred to some section of 210 or 211?

URATANI: No, documentation means that,

for example, you have it on a piece of paper saying that on this date you have installed and, if it is installed by the vendor, the vendor certifies that it has been installed.

CALLAHAN: A lot of this we would be doing anyway under just good practices.

URATANI: Yes.

CALLAHAN: But it sounds like this is very codified and very spelled out, and someone is going to come in and ask us for our OQs or PQs. I just wonder where it says we have to do this if we were following this document. I just don't see it in there.

URATANI: You mean that it is not spelled out?

CALLAHAN: You sort of go into this lingo that very much relates to, you know, enforcement of GMPs but I just don't see the transition to the PET GMPs that we are talking about today. See, I just don't see where it is spelled out, where it would be known to us that we have to provide all this documentation as you defined it.

URATANI: So, maybe we should clarify it in the guidance document.

CALLAHAN: I don't come from a GMP

background so this sounded like a lot of new language and abbreviations.

URATANI: I am sorry that I confused or maybe scared you with a lot of Qs, but basically the bottom line is that your equipment should be qualified to make sure that the result you are getting is reproducible and meets specifications and is reliable.

HUNG: This is Joe Hung. I just want to make a simple comment on page 13 with regard to the dose calibrator. The current NRC new regulation, under Part 35.60, they only required the calibration to be followed--you have to follow nationally recognized standards or the manufacturer instructions. So, all the description has been removed from the current NRC regulations.

URATANI: Ravi, would you like to comment on that?

KASLIWAL: So, what are you saying we should do? We should delete the reference to NRC?

HUNG: I think the new NRC regulation on this particular issue is 10 CFR 35.60.

KASLIWAL: Okay, we will take a look at it.

FERRIS: To get back to the previous

question with regard to equipment qualification, what you are asking for then is a validation protocol for new equipment prior to the time you initiate IQ, OQ and PQ. That would be for new equipment. Would you require retrospective validation protocols for equipment that you currently use?

URATANI: Well, the equipment that you already have in your PET facilities, of course you do not need to do the installation. All you need to do is operational qualification to challenge the limits to make sure that your equipment is operating, and also when you do your process that is your performance qualification. We don't call that validation. We call it qualification because validation would be more like--

FERRIS: What is the difference?

ZIGLER: Brenda, what I think Bob is highlighting is and what Ron was saying is that we need definitions for qualification but they need to be in the context of other items that are discussed in the guidance document, for example, verification, system suitability and validation. One definition shouldn't exist outside the other one, and somehow we need to know how they all fit

together. Maybe it is not appropriate to use some of those terms.

URATANI: We will make a clarification, sure.

KASLIWAL: I might want to point out that on page 11 of the guidance it does indicate provision for existing equipment. It is the second paragraph of page 11, 462 to 466 I think.

SWANSON: Brenda, can I ask another question? On page 11, under automated radiochemical synthesis apparatus, you say that prior to production of a PET drug product batch, the operator should conduct a performance check to ensure the following, and you have the monitoring and/or recording devices, temperature, pressure and functioning properly. How would you see us doing that?

URATANI: Ravi, you want to take that?

KASLIWAL: I guess it would depend on the device.

SWANSON: Okay, an automated synthesis device. You are familiar with them, Ravi. How would we do that? I mean, I think right now, sure, we go check and see that the temperature recording devices have the right temperatures for a synthesis

process, but what steps would you have us do to make sure that those temperature recording devices are, in fact, functioning properly? A second measurement? Is there a temperature standard?

KASLIWAL: No, whatever your manufacturer recommends for that.

SWANSON: Whatever the manufacturer recommends? I doubt they have any recommendations for that, Ravi.

KASLIWAL: Then I guess for your facility, whatever works for you, you make those up and you follow them. You establish those procedures.

SWANSON: That is what I am asking, what would an example of those procedures be?

KASLIWAL: Well, it depends on what you are doing. SWANSON: I am trying to make sure it is functioning properly.

EMRAN: I think one of the questions was asked already by Bob regarding retrofitting the existing equipment. But it doesn't spell out here how we are going to do that, maintained and calibrated according to written procedures. How are you going to inspect us regarding this?

URATANI: Which line number is that?

EMRAN: This is on page 11, 462 to 466.

URATANI: What is the question again?

EMRAN: How are you going to handle this? What kind of documentation do you need to see in order for us to prove that we have been maintaining performance qualifications?

URATANI: Normally, you would have a procedure in place in which you say that for this piece of equipment, especially a major piece of equipment, for example, you will do the maintenance like once every six months. You know, you specify the frequency, and then you also have a procedure saying what will be checked, and the documentation will be another record to show that you actually did it and what has been done, what has been checked.

EMRAN: This whole process that we are discussing now applies only to commercial products and equipment that we purchase. What about equipment that we develop in-house? Most of us are doing that right now.

URATANI: You mean the synthesizer?

EMRAN: Yes, we built our own synthesizer, our own analyzers, and so forth. So, how are you going to handle those?

URATANI: Are they automated?

EMRAN: Not necessarily. Some are automated.

LEUTZINGER: Ali, I would imagine you would probably try to have some standard operating procedures for any person, technician or someone who is going to run that equipment.

EMRAN: Absolutely. When we develop anything we write up the history for that equipment, how we developed it and so forth, and then how we are going to operate it.

LEUTZINGER: I would imagine an inspector who is going to come in and look at your facility probably would want to see what you have in place for standard operating procedures.

EMRAN: So, you would look at the history that we have and that would be satisfactory?

LEUTZINGER: I don't know if it is satisfactory but I would imagine they would probably want to see that.

URATANI: I don't know exactly the specifics. I think we need to think about the specific situation that you are talking about. I am not quite clear.

EMRAN: Well, the PET industry is in its infancy. We are not stopping with FDG. We are

developing a lot more radiotracers and equipment to go with these radiotracers. They could basically be the same as an FDG unit or modified a little bit, and so forth. So, because of the dynamic nature of the industry, how are we going to handle that, how the FDA will look at that favorably because we can't spend that much time and effort with equipment that is not commercially available or commercially invested for. l

LEUTZINGER: But, Ali, part of that is up to you. If you are saying that you have a facility that is under control where you are making a product, it is up to you to have whatever you need to have in place, standard operating procedure or some kind of procedures that are written down, documented, for how you are running the operation to show that it is in control. So, part of this is really your responsibility and inspectors then will probably look at that sort of thing and see what you have and whether you do have something in place to show that you can maintain control of an entire production. That would include analytical equipment too for QC.

KASLIWAL: One other thing that I want to point out when you are saying home-made equipment,

you can make equipment and I don't particularly see anything wrong with that, but obviously equipment performs a synthesis operation in a given fashion for which you have a standard procedure which you have submitted in the NDA and you got an approval for. That is what is what you are going to be inspected against, whether your procedures do the intended job and whether that is what you have been following. You can't make any ad hoc changes, if that is what you are asking.

EMRAN: I agree with that but we need to make this clear because we will agree on everything here but the inspectors will come in, and they don't have the background that we have with such a meeting, and they will come up with personal interpretations. So, the language needs to be clear regarding that so the inspectors will understand where we are coming from.

CONTI: I have a comment on the calibration issues also. Many of these pieces of equipment have calibration parameters provided by the manufacturer when they are put into operation. Certainly, they are not appropriate to do each time one uses the equipment. How do you make that distinction?

KASLIWAL: If the manufacturer is recommending that you do perform the calibration check after you turn the equipment on, if you are turning the equipment off and turning it on in the morning, I think you need to follow the manufacturer's directions.

CONTI: But in the installation could be when you turn it on, you need to do this. Does that mean that automatically when you turn it on you need to do it?

KASLIWAL: It depends how the manufacturer is recommending it, whether on installation--I mean, for example, you do daily calibration checks.

CONTI: Yes, there are some things that we have to do by other requirements on the basis of our state--

KASLIWAL: Right, and if you think your equipment functions without a check, you know, you need to assure us of that and, you know, we obviously will look at what supporting evidence you have for that. Certainly, if the manufacturer is recommending something, you need to follow that.

CONTI: I would think it would be focused primarily on preventive maintenance issues or routine checking of equipment.

KASLIWAL: Right. See, routine--it depends on what equipment. You know, I don't want to make blank--it depends on what equipment. You could set up your procedures to do periodic--but, you know, you have to have that in the written document and follow that but it is up to you how you set it up. I mean, there is guidance available from USP, from manufacturers, from FDA guidances in general. I mean, in the literature there are guidances available.

WATKINS: Len Watkins, from the University of Iowa. Could you give us some examples of your high and low limits, for example, in the synthesis module? What sort of parameters are you expecting us go look at there? Most of the pressures and temperatures are controlled. We don't have limits per se.

URATANI: So, you are saying that you don't have limits for high and low temperature?

WATKINS: If we are doing hydrolysis and we do it at 130 degrees; we don't do it at 100 or 150.

KASLIWAL: I mean, I don't think anyone would intentionally do it. The intent here is if your heater goes wrong, and you are doing it at 170

degrees or 180 you ought to be able to capture that.

WATSON: Well, I know you have a problem with final product analysis. It seems to me that that is the important issue, does the product you get at the end have any differences? Whether the temperature is 125 or 135 the product you get is still the same.

KASLIWAL: Right, and what I am saying is, I mean, there are in-process controls that are meaningful and there are in-process controls that may not be meaningful and you will define that in your application and you follow that.

WATSON: I just bring it up because you say high and low limits--

KASLIWAL: In sugar molecule, I mean, if you wait too high for long, I mean, you will form caramel. Right?

WATSON: Absolutely, and you won't get your product.

LEUTZINGER: I just wanted to comment that we are not suggesting that every single operating parameter needs to be controlled and adjusted on a daily basis. You need to identify the critical operating in-process and process controls, and

those are the ones for which limits need to be set.

JACKSON: Mark Jackson, GE Medical Systems. As long as we are talking about equipment, I would like to ask about the software aspect of the quality control equipment and what type of validation will be required on the software compared to normal pharmaceutical requirements for something like chromatography software. Will you hold us to the same standard? We will have a three to five year grace period to bring the software validations up to normal pharmaceutical specs, or what will be the FDA's intention on that?

URATANI: Well, as I stated at the very beginning, if that software is available right now, if it is common software, I expect you to have it but we do understand that there will be a delay in compliance with respect to the software validation, and we will exercise our regulatory discretion on that and will allow you some time to come up to speed.

JACKSON: Thank you.

KASLIWAL: Can I also comment? I mean, you may have three to five years anyway to become compliant--

[Laughter]

MOSLEY: I am a little confused. David Mosley, Eli Lilly. My understanding was that radiology software was exempt by the 1978 Act of Congress. Could you please specify what software you will regulate and what you won't?

KASLIWAL: You mean radiology imaging?

MOSLEY: Yes, and related software.

KASLIWAL: I don't think so.

LEEDHAM: Dr. Mosley, I think what you are talking about here is radiology software that was used with cameras and devices on the market for medical devices prior to 1976. What we are talking about here is not classified as a medical device; it is classified as part of the manufacturing process, manufacturing equipment. Therefore, it is a different issue.

HUNG: So, is it fair to say that as long as we follow the manufacturer's instruction in terms of the usage, in terms of the calibration of the equipment that will be okay with the FDA? It may not be the same as what you say in the guidance. In what way does it differ? Could you point to it? Like you say, it depends on the equipment?

CHALY: I am Thomas Chaly, from Northshore

University Hospital. This is regarding the black box and the validation that you are talking about. Most of the black boxes that are available are completely controlled and the only thing you can do there is a validation of your own, saying that you can take the temperature, whatever it is, using separate control once in a while. The main thing is the quality of the product that is produced. We can validate the machine on the basis of the quality of the product that is produced.

URATANI: Basically, we are saying that you qualify the process of producing the FDG, let's say, and it will be a production process validation.

CHALY: Because it is very difficult for us to check at each step what pressure is there and what temperature is there. It will be hard to do that. The only thing that we can do is we can write up a validation procedure in our center based on the equipment that we have, and then we can follow that one in our center, and the main validation should be based on the product that is produced by the instrument.

URATANI: Yes, and this is going to be discussed later on.

BARRIO: We have a common denominator here in regards to the previous discussion. You know, we would love to see some sort of SOP for whatever instrument, production process or whatever will suffice, and the validation based on the quality control of the final product, and yields being reasonable could be the other side of the coin of course.

I appreciate the comment in regards to critical elements of quality control. The synthesis procedure has to be controlled and understood, you know, who wants to operate with an HPLC that doesn't work? We need to make sure, you know, that the apparatus is working. However, the word "critical" I think may have different interpretations because the language in this document may be contradicting that description of "critical." For example, you wonder, in line 550, what the temperature and humidity of the dry heat oven refrigerator/freezing and incubator would do for synthesis of FDG. You know, clearly, it may be important if you have your precursor standing in that freezer and the freezer is not working anymore but you clearly will now. It will be obvious to anyone. But the thing that scares everyone is if

one doesn't have written records about the temperature, the freezer or the refrigerator, what is going to happen? Those are the kinds of issues that are important. I think if we define very clearly in writing that we are talking about standard operating procedures, certain performance for analytical equipment or synthesis will suffice, I think we will understand that language very well. I think it would be helpful to have these statements in and remove anything that appears to be essentially superficial or unnecessary because that produces some discomfort in all of us who read this.

LEUTZINGER: We are only interested in those parameters that, like for an HPLC or GC or other analytical equipment--we are only interested in the fact that your machine works. First of all, you really should have some sort of maintenance program to make sure that you keep all that equipment working. I am an analytical chemist, and it is very easy to tell, for example, weeks before that your instrument is starting to degrade and you should have some sort of track record, keeping track of the results on your instrument.

The advantage of having a standard

operating procedure partly satisfies that, those particular needs, and you should follow that. But the GMPs, as far as I am concerned, have to do with you document what you do and you do what you document. I think that is what the whole business of good manufacturing practice is in my estimation.

So, standard operating procedures are really important because it gives you a road map through the use of your equipment and it really helps you to prevent surprises. Nobody is interested in surprises. You don't want a surprise. As long as you follow those procedures and are diligent about maintenance, then I think you will minimize those procedures and I think that is all really that we care about in the FDA, that you have something in place that shows that you have a production process that is under control, and I think that is really what it comes down to, and I think that is what any inspector who is looking at your facility is going to be interested in.

BARRIO: Yes, I appreciate that. I think that is exactly what logic will indicate and that is what we already do. Essentially, we all know, whatever system we have, whether the systems are

working or not; the quality control equipment is working or not. I am talking about some extra documentation that appears to be required in some circumstances that may not really necessarily conform to your general discussion.

CHALY: Thomas Chaly, from Northshore. I don't think that the temperature and humidity and dry heat validating is necessary on a daily basis for a dry oven. I don't know whether that is essential. If you validate once in a while and you check the performance of that, that should be more than enough.

Another thing I don't understand is prior to use the analysis should make sure that the GC system is functioning correctly. I don't know what you mean by that. What do we have to do for that?

URATANI: Which line?

CHALY: It is on page 13, 563, prior to its use, the analyst should make sure that the GC system is functioning correctly. What do you mean by that? I don't understand that? We validate the GC.

KASLIWAL: You validate the method.

CHALY: The method, right.

KASLIWAL: And then when you perform, what

if the GC is not working? Where does that validation go then?

CHALY: No, what we do is we validate GC and every day we perform the analysis of the sample, and if you see something abnormal, then we will validate again. If we see the same thing and we are getting an expected result, I don't see the need--I don't understand why the equipment has to be verified.

LEEDHAM: Do you have a starter procedure for when you start the equipment in the morning or when you are using the equipment?

CHALY: If it is turned on, there is a procedure.

LEEDHAM: And are there any parameters you need to check before performing--

CHALY: We have to make sure that all the gases are flowing. We have flow gauges on each gas tank. Those things we can check, but you are stating here with this sentence, prior to its use, the analyst should make sure that the GC system is functioning. So, we have to do something to perform that?

LEUTZINGER: How do you know that it is working properly from day to day?

CHALY: By inserting a sample, we can see that.

LEUTZINGER: Maybe that in itself, some sort of an initial sample, can serve as a means. I mean, we usually ask for a system suitability test which means there is a standard that you would inject into the GC, HPLC or whatever--

CHALY: You are saying that we ought to insert a standard--

LEUTZINGER: We generally ask that. That could be at the beginning of the day. See, the whole idea is it gets back to how do you know. I guess you know because the peak has the same retention time--

CHALY: Yes--

LEUTZINGER: So, what happens if it doesn't have the same retention time? Then what do you do?

CHALY: If it doesn't have the same retention time, then we will go back and validate again before we do the analysis.

LEUTZINGER: Well, the idea of having a system suitability test is partially tied to this idea of maintenance of the chromatograph.

CHALY: The problem is that we are not

just doing GC alone; we are doing HPLC, we are doing TLC, we are doing ten different tests and if you are insisting that we have to do testing for each individual equipment like this, there will be a pile of documents that we have to submit every day.

LEUTZINGER: Yes, I understand the problem. Possibly you can work it out. I don't think I have any problem with having sort of a suitability test built into the actual test run that you do.

CHALY: We have an operating procedure and we have a validation procedure. We do all these things, and we are testing this equipment like our operating procedure, once in six months or something like that. If we see something abnormal, we do it right away.

LEUTZINGER: Well, I am glad you do that.

CHALY: That is why I am saying this kind of sentence will be confusing.

LEUTZINGER: Well, it is because in the analytical field we generally ask people to have a system suitability test. Most analytical laboratories do, in fact, have some kind of a system suitability test for whatever equipment they

have. It is part of maintenance. It is a maintenance kind of program, but there is flexibility in this thing so you can work it through, say, you have records every day of runs that you make and you can somehow work your system suitability testing all within the same business of running the sample.

ZIGLER: Eldon, what would you expect to see in a system suitability for a gas chromatograph?

LEUTZINGER: For example, you might see the intensity of the peak at a certain standard of expectation. You might see, say, the peak width--

ZIGLER: You mean in terms of the number of injections, that sort of thing. Would you expect more from an injection?

LEUTZINGER: Well, this is always a problem. If you run an analytical laboratory day by day it is easier because you see its performance day by day, keep a log book of it. You keep a log book of it. You see how the instrument is performing day by day. You can recognize right away if there is some kind of a problem. At the beginning of the day, usually a good analytical laboratory will have some sort of a system

suitability test, a very simple test where you are just looking at, say, intensity of a peak that is coming out or the peak width, shape, you know, do you see some irregularities in the shape of things? I would think you would want to know that before you put a sample through there and all of a sudden, hey, my machine isn't working anymore, so what am I going to do with the sample? Maybe your product is perfectly good but you wouldn't know it from the chromatogram. The chromatogram looks bad. Is that because the product is bad or is that because the analytical run is bad? So, you have some idea of what that is before you go in there and can avoid all this problem of, well, what am I going to do with this product now? I have to release it but the chromatogram says there is something wrong with it.

CONTI: Another way to potentially handle some of these issues is to work it into a QA program that we talked about earlier, as opposed to doing it on a daily basis for a very infrequent occurrence, again going back to track record issues on the pieces of equipment that you have.

LEUTZINGER: Yes, very definitely there should be a track record. Any good analytical

laboratory is going to keep a good track record, a book of chromatograms. That is what I do, a bunch of chromatograms day by day so you know exactly how it is performing.

CONTI: Going back to something tangible, and maybe some of us remember in hospitals, if you look at a parameter of hospital performance activity, let's say number of x-ray films that are replicated, and if you gather the data and show that the frequency is X and you set a threshold, and if it goes above that you then look at that as a performance criteria and you follow that until the problems are corrected, but you don't necessarily have to do it all the time for every single run. You look at it, in the event that it does happen, whether it exceeds a threshold that you expect.

LEUTZINGER: Right. I wouldn't recommend that necessarily you have to do it every time you run a chromatograph but you can do it at the beginning of the day if you know that you are going to have a whole bunch of analytical work to do on that particular day. You could do it early so if you knew that there was something wrong with your instrument you could avoid having to go through the

whole day making these things and then wind up not knowing what to do with them. It might give you some lead time to get the instruments fixed. So, you wouldn't have to do it every time you run the chromatograph but you could do it at the beginning of the day, for example, on a heavy day.

CONTI: In large measure, the regulation should sort of say that the facility should adopt an appropriate quality assurance program that meets the needs and expectations of the equipment being used in that facility, and the known track record of activities in that facility.

LEUTZINGER: I think that really would be a great idea, yes.

CONTI: But you would have a lot of flexibility to set up your own program, and you don't have to deal with whether I connected the tubes properly if you don't feel that is appropriate.

LEUTZINGER: Yes, whatever it takes, and that is all a part of showing the inspector that, say, your facility is working under control.

KASLIWAL: I just want to point out that generally most quality control procedures would be approved as part of your application, and you need

to describe exactly what you need to do for the quality control, and you need to follow that.

DUFFY: I think I am hearing that you are suggesting--by the way, I am getting some dirty looks from over there; I didn't identify myself. I am Eric Duffy, with the chemistry division. We might revise the guidance to specifically say that an appropriate program should be established that on a periodic basis this should be done. Is that what you are suggesting?

CONTI: I am suggesting that a facility should define what should be done.

DUFFY: Right, we will take that under advisement and consider some revisions here. I did hear one specific one under temperature control recording devices, that it be done on every work day and the suggestion, I believe, was that maybe less frequently than that would be appropriate.

CONTI: But if you don't have a temperature control problem in ten years, whether you need to monitor that every day or once a year or once every six months, you should have some reasonable period.

DUFFY: We will consider some alternative wording I think.

CHALY: Thomas Chaly again, from Northshore. I think there is no problem in taking GC. I agree with you that GC should perform very well, and we are doing the best we can to do that one. But the problem is that we don't have just the GC; we have HPLC, we have TLC, we have osmolarity. All of this, if we have to validate, that is too much for one person to do.

LEUTZINGER: We are not asking you to do that every time you do--

CHALY: No, to test the machine on a daily basis is too much to ask.

LEUTZINGER: Like I said, do you have to use all those particular instruments on the same day?

CHALY: Yes.

LEUTZINGER: Maybe the idea of the QA program is something that is applicable in a situation like this.

CHALY: Because then we have to check--

LEUTZINGER: We are not asking you to do anything unreasonable.

CHALY: No, no, no, I completely agree with you that the machine should be working. The GC should be working, but it is quite unnecessary

to check every day. Now, if we see that one peak is not coming in the right place, then we will go back and definitely check what is wrong with the machine. We will repeat that.

LEUTZINGER: Yes, I believe you.

CHALY: Thank you.

ZIGLER: Brenda, I have one question on line 581, under dose calibrators. It mentions the use of the word "printout." Do you mean literally that the machine must make a printout?

URATANI: Well, I don't think there is such a requirement.

KASLIWAL: Can you repeat that?

ZIGLER: On line 581, under dose calibrators, you mention that the device must be capable of a printout. Do you really mean a printout?

KASLIWAL: Some kind of automated--

ZIGLER: Can we just read the display and write it down?

DUFFY: We are talking about output.

ZIGLER: Thank you.

JACKSON: Mark Jackson, GE Medical Systems. Can I just ask, Eldon, the suitability tests for each one of these instruments are in the

USP for each one of these quality control tests, and in the chromatography section is the suitability and reliability check a way of doing it, and the procedure is already written for most of these things, and those will be good enough if we follow those, do you think?

LEUTZINGER: Possibly. It depends on what the test is intended for. All right?

JACKSON: Exactly for these instruments? The quality check for each daily test, or whatever, in the USP and the chromatography guidance--

LEUTZINGER: Yes.

JACKSON: --suitability for a TLC scanner, a GC, an HPLC, and I just think they should refer to that in writing their standard operating procedures.

LEUTZINGER: I am glad that you have noted the GC chapter of the USP, that is very good.

URATANI: Moving on in the interest of time, let's go to production and process validation. So, basically, for process validation what we are requiring is that you establish procedures and specifications, and with regard to production, we give some detail about the master production record and batch production records.

For production process validation, you can do it either retrospective, prospective or concurrent. Is there any question on that? I think it is explained pretty well in the guidance.

BROWNLEE: January Brownlee, from SYNCOR. Most of the current documents on process validation--I am referring to ones like from CDRH, international documents from ISO, the global harmonization test document on process validation which, by the way, is the one that talks about IQ, OQ and PQ quite extensively, all of these documents go on to define process validation as something that needs to be done when you cannot 100 percent test and inspect the finished product to verify that the process was valid. Here, we have a product where we are getting one vial, we are testing it every time and so, in essence, every time we make a batch we are validating that that process is effective. It leaves me wondering why we need to go back and do a retrospective validation when, in fact, we have validated the process with every single batch because we are doing 100 percent test inspection on every batch.

URATANI: Well, the principle of GMP is to build quality into the process. I think a lot of

times with the end product testing you might not be able to see everything. Plus, another thing that I would like to point out is that you some of you have requests for release of the product, some of those PET products with very short half-life, like C-11, and you want to be able to inject it into the patients without finishing all the end product testing. For this, I think that you really need to have a validation process.

BROWNLEE: What kinds of things will you be looking for then in a retrospective validation?

URATANI: In a retrospective validation, basically, we are looking at the established history of your manufacturing process. So, you will have to do a comprehensive review of your accumulated data--

BROWNLEE: Which would still be the final test results.

URATANI: --and show that that particular process that you have cumulative data on is capable of producing results that meet the specification and produce a quality product, but then it should have a written procedure so that we know what you are validating against because whatever data you accumulate over, say, the last two years, you might

have changed the procedure several times, and whatever procedure you are using currently, that is the retrospective validation that we are looking at.

KASLIWAL: Brenda, maybe if I can clarify a little bit here. Whether you want to do prospective validation or this other validation is really up to you. It is a provision provided to you in case you want to do that. But if you want to make three batches and do that kind of approach, that is fine. In terms of what you are testing, validation should incorporate complete testing because not every test is a finished product test. You are not completing every test prior to release, not necessarily. Okay?

BROWNLEE: What other kinds of tests then would you be looking for?

KASLIWAL: For example, let's say in FDG, like a chloroxyglucose test so validation batches should have data on those which you are not necessarily doing.

CONTI: Again, those things could be done under a quality assurance program where you periodically check these types of parameters, not necessarily to validate process control but to

assure that you are going to produce the product given the fact that you are testing each end product. So, if your track record demonstrates that it is below a certain threshold established in your QA program, there is no need to do this very frequently and then one can skip and look at different portions of the process on a periodic basis, again, integrated into the same quality assurance program.

KASLIWAL: After the initial, yes.

SWANSON: I think one of the areas that the guidance document is deficient in, and we could use some guidance on, is that it doesn't clearly address those types of things that we ought to be looking at in validation studies versus what we ought to be looking at on routine batch quality control. It is something that we went into a fair amount of detail on in the USP chapter and it just did not get brought forth into this document. I think that, in fact, is some pretty good guidance that the community could benefit from.

HUNG: I have a question about the batch record. If you decided to use the computer to keep the records, how much do we have to stick to the 21 CFR Part 11, talking about electronic records? Do

we need to verify the computer system to make sure that it can perform the job, and also the issue I brought up this morning about the time stamp and audit trail system?

URATANI: The batch records, I think right now there is commercial software available which you can add on to the existing computer program, which has an audit trail capability.

HUNG: But do we need to verify the commercially available software to make sure that it can do the job?

URATANI: Well, I guess you do. I think you do have to verify anything you buy. You want to make sure that it is doing the job.

HUNG: So, any commercially available system that would be recommended by the FDA? If so, could you be more specific and mention those names?

URATANI: I don't think we are in a position to recommend any brand name. But I know there are commercial programs available.

BUHAY: Nick Buhay, from the GMP Division. Part 11 addresses the preparation of electronic records. So, wherever an electronic record is used in complying with the requirement, the Part 11

applies. There are a lot of these specific requirements within Part 11 for what a system that produces electronic record ought to have, and one of them is use of an audit trail. This is a new regulation. In terms of finding out the kinds of systems that are in use, the industry that prepares these programs is very much in the mode of investigating how they can comply and produce products that they can supply that will comply. We have a program and a person is dedicated full-time to working with that industry and working with the user industry to come up with rational judgments on meeting those requirements.

In the meantime, we are in a situation of recognizing the status of the new regulation, legacy systems and also responses that are going to be--the technology that will respond in developing programs that will produce and meet the requirements. So, we are just suspending enforcement in a very bureaucratic way. We are very much tolerating and looking at what efforts are being made, and just simply looking for the industry to respond to this new requirement while we, ourselves, are assessing it.

There is a program for generating guidance

in this area that is going on and separately you should be seeing those in terms of these requirements, time stamping and should it be in Greenwich time or should it be in local time, and all the other issues, validation if you transmit a record through the internet, how does that impact on the validation of that program because of the way the internet operates, and all those other issues. We are trying to face those one by one as they come up.

MATTMULLER: Steve Mattmuller, from Kettering Clinical Center. This is for Brenda. In regards to software systems, as a small lab, as you can well imagine, we haven't spent $30,000 for HP software for GC that is validated. I am encouraged, in the guidance document, that you talk about if your computer system can operate your FDG synthesis box three times the same way in a row, then that is considered validation. Would that same test then be applicable to, say, my GC or my TLC unit?

URATANI: Yes, except the computer--well, there are two parts to it. You know, you are talking about computer validation of the process using a GC or the black box or the HPLC, but there

is also another part which has to do with computer validation of Part 11 compliance of record keeping, which is a separate issue.

As far as record keeping is concerned, we want the software to have the capability that the records cannot be deleted so that corrections made to records have history of what is being changed. That is different than the other computer validation that you are talking about which has to do with the process. Whether the process is able to produce a result is different.

ZIGLER: Brenda, can I make a comment about process validation in general again?

URATANI: Yes.

ZIGLER: I wanted to reemphasize a point that was made at the microphone a second ago, and this is one of the key things that separates PET from traditional pharmaceuticals, and that is we make one vial and we test 100 percent our products. That brings a level of control that is higher than where you only test a certain portion of multiple vials. All I want to say is that the process validation expectation should be reduced accordingly because of that. We need to build quality into our products. There is no doubt about

that. It just needs to be commensurate with the fact that we are testing 100 percent of our end products.

I also wanted to repeat my comment earlier about when we deal with these definitions of validation, verification and qualification, suitability, they all need to be done in one context; they can't be separately defined, they have to be defined together.

KASLIWAL: Just a comment on that, you know, for the most part I agree with what you are saying but understand also there are instances, for example, in sterility you don't finish that, although there is an alternate method but let's say with C-13 you may not be able to finish. So, there is some level of previous control and validation. It may be a different kind.

MATTMULLER: I have a follow-up question to my previous one. For a specific example of our GC, we run a standard three times and get the same result each time and we print it out three times. Would that then be sufficient as far as satisfying your concerns for having a record that wasn't modified, corrected or changed afterwards? If we have a hard copy printed record of everything that

the software system collected, analyzed and printed out?

URATANI: I think so.

KASLIWAL: If you maintain a hard copy, then your electronic trail issues go away.

SWANSON: I have a question related to a statement on lines 880 to 887, dealing with batch record. It says the batch record should be a check list documenting that all processing steps and their controls were carried out, timed events occurred within specifications, heating steps occurred at the specified temperatures, and ingredients were properly transferred into the reaction vessel. In order to document that certain of these things occurred, like ingredients did in fact transfer into the different reaction vessels, would require that we actually observe the process, which is typically not possible for many of the synthesis units and would certainly create a radiation exposure concern.

URATANI: I think you do the production every time and you know the process intimately, so you should be the one who determines whether it is feasible or not because what we are putting in here could be general, and maybe we did not take into

account the radiation concern. You should be the one to tell us whether that is feasible.

SWANSON: In essence, that is what we are telling you.

URATANI: Okay, I got it.

HUNG: Some of the commercially available black boxes actually have that kind of in-progress control so you should be able to observe that progress without even having to open up the black box. It is all documented in a real-time manner.

URATANI: Right. I guess it depends on the equipment that you use. Some is more sophisticated than other. Some may be able to tell you right away and for some, I don't know if you have to do something else to know what is going on. So, it is on a case by case basis and you know your process better than us, so you are the one to tell us.

KEPPLER: I think one of the issues though is that it is not as if we are going to stop the production process and continue on if one of the transfers didn't occur. So, to watch it and to observe a transfer occurring isn't going to change anything. It either finishes and has a product at the end, or it doesn't. I think that is what is

missing here. We have all these, you know, step by step checks that we are supposed to sign off on throughout the process when whether or not it happens won't matter because we will either have the dose at the end or not. So, why have all these interim checks that this occurred at this time and that it transferred appropriately when you can't change it if it didn't?

KASLIWAL: Again it comes back to you, you make the decision whether it is a critical parameter to control or not.

KEPPLER: But they are specified in here as critical parameters.

CONTI: Again, it gets back to the issue of if you are going to test every batch you need to identify if there are additional parameters that would not be tested in that final batch that are critical to the process, and only do process control in those areas. I think that is a reasonable alternative to the complete list of process controls that are cited here as examples. If you test every batch and the only other thing you are ever worried about is chlorinated glucose analog, then if you do an appropriate quality assurance procedure and show by track record that

you don't have that occurring, that is it; we are done. We don't need any other process control if that is the only critical step. So, it should be written generically enough that it takes into account other PET radiotracers. So, simply state if you test each batch and you take into account any other critical factors with the given pharmaceutical that need to be evaluated with process control, have the cite and put it in. End of story.

KEPPLER: Can I ask for a definition of critical step?

URATANI: I think critical step is for you to define, not for us to define.

KASLIWAL: I think anything that might affect the identity, purity, quality and strength of your drug product.

KEPPLER: But that would be everything.

CONTI: That would not be achievable through end testing, you could not get that through end testing of the final product. That is the key.

KASLIWAL: Certain quality parameter you are not testing.

CONTI: Then those are the ones you use the process control for. That is my point. I am

trying to identify which things that you are concerned about that are going to affect patient safety, that need to have the appropriate process control, that are not achieved through end product testing.

KASLIWAL: So, I don't think we have an argument.

LEUTZINGER: That is what you have to do. I mean, you have to identify what those critical points are. That is part of your responsibility. These are just examples. I mean, it is a guidance document and, after all, it is not telling you, you have to do exactly this.

KASLIWAL: Basically, when you are deciding that, these are the sorts of things you may want to consider, and you may reach a conclusion that that is not important.

CONTI: Unfortunately, it is really written towards FDG and not generically enough to give us enough flexibility to do what we see is necessary, and it does still beg the question that Dennis Swanson brought up earlier about what becomes de facto regulations when you are dealing with this on an inspection. What are they looking for? The guidance is primarily focused on FDG.

LEUTZINGER: This is a guidance document.

CONTI: I understand that, but it depends on how it is interpreted.

AXELRAD: But I think it really does depend, and I think that we need to go back and look at this. We know a fair amount about FDG and how it is produced. We have written a sample--whatever it is called, a template application and a guidance document on that. So, I think that we need to clarify where we are talking about FDG. Maybe we can give examples of what we consider to be the critical steps so that you can have a better understanding of how we are determining what a critical step is. Obviously, this will have to evolve so the inspectors are given guidance or examples of what we think are critical steps that we think need to be documented.

CHALY: This is Thomas Chaly from Northshore. There are many critical steps in the synthesis, but if one of the critical steps fails you won't get the product. For example, I can tell you that in one of the synthesizers that we are using, if the sodium hydroxide cylinder doesn't come down there won't be any hydrolysis.

CONTI: But those that affect patient

safety, not whether you have a final product or not. That is the difference.

CHALY: No, what I am saying is there won't be any product.

CONTI: That is not necessary to monitor per se. So, it may be critical in terms of actually producing the drug--

CHALY: Then what is critical?

CONTI: The safety of the final product--

CHALY: What is the critical point of the synthesis then?

CONTI: Efficacy of the final product that is not satisfied by the end testing.

CHALY: No, what I am saying is what is the critical point in the synthesis then?

CONTI: I gave you an example of a chlorinated species and the fact that if it doesn't exist--

CHALY: Chlorinated things are not found in all FDGs.

CONTI: Well, if you have documented that and you have a track record, you don't necessarily have to check that routinely. You may check it periodically, once a year or maybe once every ten years. The point is that whatever is not achieved

through end testing of the final product that you are concerned about, that would affect potentially patient safety, you can design a process control to look at.

CHALY: Can you give some examples of what are the particular steps in that synthesis?

CONTI: I just gave you on, chlorinated--

CHALY: That is what I am saying, there are many synthesizers that are not using hydrolysis with HCL. When you use that you are expecting a chlorinated compound.

PARTICIPANT: You have to worry about mannose.

CHALY: You have to devise a different test for that.

CONTI: Then your facility deals with mannose.

CHALY: No, what I am saying is there are not that many particular steps that you can say--

CONTI: That is the point, there aren't that many. That is why we feel end testing is the way to go.

CHALY: Okay.

CONTI: Unfortunately, that is not the consensus. What I am trying to say is that if

there are other areas that are important we need to identify them and focus any process control on them.

DUFFY: I just wanted to comment on the notion that the only way of defining a critical process parameter is that which might affect patient safety. I don't think that is really the consensus view. Those controls that are necessary to have the process operate as is intended is really more to the point, and it is verified through end product testing. That is the notion of validation and GMP controls.

CONTI: So, is that any different really than what we are saying? If the end product testing achieves the same goal, what other parameters do we have to look at to show that the process is working?

DUFFY: Well, that is something that you need to determine for your particular process. This gentleman feels that, for example, the rate of hydrolysis--the addition of hydroxide is a critical step to effect the process properly. For your particular processes you may feel that, through the validation of your black box for example, you have covered your bases and you need not then have

routine in-process controls. This is something that you need to determine on your own and have data to substantiate. That is really all.

KEPPLER: But that gets back to my question. You know, I think we have come full circle here because it gets back to my question, why have a process control that looks at a critical step, which is the temperature of your vial, when it is not going to change anything? At that point it is too late to salvage the batch.

DUFFY: Well, if you make the determination that it is not, in fact, important to observe that, then apparently it is not a critical operating parameter for in-process control.

AXELRAD: I feel like we are going around. I am sorry I was gone for some period of time, but somehow we seem to be going in circles here. I think that we need to get comments. I think we have been hearing a bunch, and I assume there were many more while I was gone, on the specific things in here that we may have identified as critical parameters or as examples of critical parameters that people don't believe are critical parameters.

I think that, because different PET centers use different processes, we can't identify

for every single process exactly what the critical parameters are. But we ought to certainly not put in here something that really is never a critical parameter, and we ought to be able to give examples of things that are critical parameters for certain kinds of processes and maybe explain them in context of whatever process. If you are using a chlorination process, this is a critical step; if you are using hydrolysis, then this is a critical step; if you are using this other process, we can give some other examples. Anyway, I think we should move on because I think we have gone around and around on this.

DUFFY: I would make just one comment just to close on that, in the approval process you interact with the FDA staff and it is through that interaction that an agreement is reached on what critical process controls are appropriate and what the batch record is going to look like. So, there is an opportunity for dialogue and presenting justification for establishing a particular batch record and process controls.

ZIGLER: Jane, could I ask a question about batch records? As I read the guidance, it looks to me like what the intention was is that the

master formulary, master control record would be a very detailed document that would basically describe everything, whereas the batch process and control record would be something that would be, you know, basically the information pertinent to that particular batch, much shorter and more concise. Is that the intention? Am I reading that correctly?

URATANI: No, the master production record actually is a template for the batch production record. So, essentially they are the same, except that the batch record will have the executed steps in when you are actually doing the production of the batch. Plus, also the batch record normally includes the testing data, the complete production of that batch.

ZIGLER: So, they would look the same except for blanks that you would fill out.

URATANI: Yes.

KASLIWAL: And your batch record will also contain the results of finished product testing.

ZIGLER: Sure. I have another question on line 1013 where it talks about the sterilizing filtration. It is on page 23, line 1013. It notes that you should conduct an integrity test on the

incoming filters before release for use, if I read that correctly. Those filters very rarely fail. I mean, there are cases of them when they fail but it would be very difficult to pick one out beforehand. So, I don't think it would really add anything to require us to do an integrity test on them prior to use. Now, once we use them, of course, we test every one of them and that is where we pick up problems and undergo reprocessing as necessary. But I think testing from that lot ahead of time to release it for use, if I am reading that correctly--

KASLIWAL: I think part of this, if I remember--I wish Dr. Hussong was here, but in part it is because you are making sub-batches where, in order to release the sub-batch, you may not be doing filter integrity testing to control the lot of those filters.

ZIGLER: I guess I am more thinking along the lines of an FDG, but that may be the case and that may be why it came up.

URATANI: I think even though in the USP Dr. Hussong has written, basically that is what we have incorporated, his draft into our document. But, for example for FDG, just do the testing after

the production because the integrity bubble points should be able to tell you whether your filter is integral or not.

ZIGLER: Thank you.

URATANI: Dr. Barrio, do you have any comments?

BARRIO: Only one, the paragraph that we have been discussing extensively, you monitor the process and, therefore, you will ensure that your product is going to be okay. In fact, what we normally do is we have a standard operating procedure and we know how the system works, and then we do the synthesis and if it doesn't work, then we go and check the process in order to see where the problem comes from. In the way it is written, I mean it is perfectly all right to monitor all these processes but not necessarily during the process of synthesis but, rather, if the synthesis really does not give you what you want. That is when you go back and find out what your problem is or came from. Of course, you will be going through all these processes to find out. For that, your standard operating procedure is that you know your system works and everything else and you don't monitor the system during the reaction; you

do it afterwards.

URATANI: We hear you. I think the next one we should go to is the laboratory control. With regard to laboratory control, we have end product release test.

KEPPLER: Brenda, we skipped control of components.

URATANI: Oh, control of components?

KEPPLER: We skipped that section.

URATANI: All right, we can do control of components first. With our new regulation, proposed regulation testing of solvents and reagents is not required. Testing of any commercial sterile pyrogen-free container closure is not required. We only require visual examination. Testing of inactive ingredients, if they are commercially approved drug products, testing is not required. However, for testing of components yielding API only specific ID test is required provided that you have established the reliability of your supplier. Other tests are not required provided that you have established reliability of your supplier. Any questions about that?

HUNG: I have a question about the API.

Do you consider fluorinating fluoride as one of the components that may yield API? If so, on page 17--first of all, we believe it shouldn't be considered as a component that can yield API but the example that you give on page 17, lines 728 to 741, in this example you only talk about using COA without mentioning the identity test. So, I just want you to clarify the inconsistency there.

There are two questions. Number one, do you consider F18 fluoride as a component that will yield API?

KASLIWAL: In which drug?

HUNG: I am sorry?

KASLIWAL: Which drug product?

HUNG: FDG for example.

KASLIWAL: FDG? If you are making sodium chloride, yes, we will consider that as API. If you are making FDG, fluoride will be considered as an intermediate.

HUNG: So, if you are talking about making an FDG you will not consider it as--

KASLIWAL: That is an intermediate.

HUNG: Okay. Then, on page 17 you actually list that as one of the examples.

KASLIWAL: I guess this is in case you are

receiving, not making your own F18 but are buying it, so you are bringing in a raw material. In that scenario, because it does yield API it is a component which gets incorporated structurally into API, so what we are saying is, as part of the identity testing, you can use your reaction base as inactivation of the first batch as the ID test.

HUNG: It is my understanding that a component that would yield API, in addition to the COA verification, you have to perform an identity test.

KASLIWAL: That is right.

HUNG: But in the example there it is simply talking about examination of COA but there is no mention of an identity test, on page 17, lines 738 through 741.

KASLIWAL: In the guidance document?

HUNG: Yes.

KASLIWAL: I think we do write that in the preamble so maybe we have to look at that.

URATANI: Yes, we will look at that. Any further comments?

SWANSON: Yes, I have a comment. Part of the relief offered by this, and I certainly think we appreciate it, is the ability to rely on

certificates of analyses for many of these things, yet we do have a problem from many vendors getting certificates of analyses because of their concerns that the FDA will actually come back and inspect them as providing the substance for potential use in humans. Is there any way that we can get the FDA's assistance in providing some kind of notification to these manufacturers to try to allow us to get more certificates of analyses?

DUFFY: Well, it is possible that we could add some things to the guidance here that provides some definitions. For example, definition of a raw material, definition of a starting material, and a statement that they need not be manufactured under GMPs. That would probably help.

SWANSON: Yes, something that we could demonstrate to them that would help us get certificates of analyses and, you know, a certain statement that that center should obtain assurance from a vendor that the vendor will report any major changes in the manufactured item. I mean, we are not going to get any kind of compliance from the vendors in that kind of a requirement unless we got some kind of a relief type of statement.

KASLIWAL: Yes. I mean, that was put in

there to help you choose a vendor. Understand, we can't force a requirement if the vendor doesn't do it.

ZIGLER: Brenda, I have a question on line 660. It is on page 15. It says the PET center should have full accountability and traceability of each lot. Does that mean that we have to maintain an inventory of our raw materials as we use them?

URATANI: No, you don't need to maintain an inventory. That is a difference from the 211.

ZIGLER: What does accountability mean there?

URATANI: Accountability means that you have a history of the incoming lot, that you document which day it is received, where, who is the supplier, the lot number. Maybe you give your own lot number, and whether you have done any examination or testing, and after the examination or testing you have reviewed those testing results and say that it is approved for use, that kind of record. That is all.

SWANSON: Another question relating to establishing reliability of a supplier. This is on page 16 to 17, lines 722 and 723. You say that the reliability of the supplier's test results can be

established by conducting independent testing and confirmation of the testing results of the first three lots of the components received, and at appropriate intervals thereafter. Does that mean that we would confirm testing results for all the specifications listed on the certificate of acceptance, or only critical ones? Would there be a different way to establish reliability of a supplier? For example, if we use that supplier's materials that routinely resulted in an end product of appropriate specifications, is that not another way to establish the reliability?

LEUTZINGER: Dennis, I think you are going to have to determine for yourself what the particular parameters are that are listed in the COA that are important. You need to have some sort of list of specifications or acceptance criteria that you would use to accept somebody's COA. I think that is the sort of thing you have to do.

SWANSON: So, basically then we would only test the product for those specific specifications that we outlined as being the important specifications?

LEUTZINGER: Yes, you need to determine what that is and that is what you would want to

follow, and that would be your standard set of acceptance criteria, testing acceptance criteria that you would then go about accepting that particular lot of material.

AXELRAD: Could we give them any guidance for the materials that we think are critical, what parts of it we think need to be tested?

DUFFY: Well, I am afraid we would have to have quite a large document to do that. I think we could possibly add some language that discusses what Eldon just expressed, which would be simply that for your particular process the acceptance criteria can be justified, and that those would then be verified for acceptance of the COA.

CONTI: Another point on that, just to repeat myself, the end product testing actually could be used as another way to confirm the COA.

LEUTZINGER: No, not necessarily.

CONTI: Could be.

LEUTZINGER: I mean, that might only do identity, but there might be something else that is in that particular lot of material. Maybe it is not in the COA but you might not be able to detect it or estimate it.

CONTI: You might not even know about it

or be able to test it.

LEUTZINGER: It is likely not going to be one of your specifications that you came up with either.

DUFFY: Let me just make it clear that we don't necessarily agree with you that it meets the end specifications verifies that all the components would meet their individual specifications. We do think that acceptance testing is necessary.

SWANSON: That is not true. I mean, you are saying you need to do identity testing. This only relates to establishing your reliability in manufacture.

DUFFY: Right, right. Exactly. What I mean by acceptance testing is the testing that you do yourself or the COA results that you accept from your supplier. Do you think we need to clarify the language here on this point?

FERRIS: Aren't you saying that in an acceptance protocol a COA is, in fact, an acceptance test?

DUFFY: Yes.

LEUTZINGER: It is only part of it.

CONTI: Identity?

LEUTZINGER: Yes. You are talking about

establishing the reliability of the supplier. I mean, once they have been established as reliable you wouldn't have to go through full testing every time you accepted that lot. You would only do identity testing and use the COA because then you would have confidence in that particular supplier to deliver a product that you knew would meet the acceptance criteria that you were expecting.

FERRIS: So then the next lot that came in from that supplier, if you just did three runs and everything was peachy, that is not acceptable as independent confirmation?

LEUTZINGER: Sure. I mean, that is the beginning. We are talking about establishing the reliability of the supplier to begin with, and once they have been established as reliable, then you are not going to have to go through full testing every time that you accept that lot. All you are going to have to do is use the COA and do an ID test.

SIMPSON: Norm Simpson, Columbia University. Since we have the internet, could not a facility do the testing and then broadcast that across the net that we can all accept and refer to that certificate of analysis?

KASLIWAL: Absolutely, it can be done centrally. We have said that all along.

URATANI: If there are no more questions with regard to this for the time being, we would like to move on and then we will take a short break after.

FEINMAN: I just want to make one point about the raw material. My name is Nate Feinman. I am with NF Chemical. We supply a COA that includes the isotopic analysis and a chemical analysis. Really, the only item that is going to be of immediate interest is the O-18 in content, which is normally 95 percent minimum. Beyond that, I mean it could be 80 percent minimum because it is really a function of the PET center. But we do provide it as 95 percent and that is the only criteria that is required today, and nothing more.

URATANI: With regard to the O-18 model, we think that the concurrent identification with product is acceptable.

KASLIWAL: He is talking about the content of COA. He is saying the only thing that they are reporting is--correct me, is enrichment?

FEINMAN: No, we are reporting the complete isotopic analysis and a complete chemical

analysis. But the only point that would be of interest in today's world is the O-18 content, nothing more. You are not going to come to me, most likely, and say, gee, what about the fluoride content or the iron content because it is really not of any interest at this point. I am not saying it couldn't be down the road as we are looking at all these parameters, but the most important parameter or the only parameter that is the O-18 content and the fact that it makes FDG is the validation.

DUFFY: That is really a point that was discussed earlier, having to do with establishing those acceptance criteria which are critical for your particular process. Yes, you are right that a more limited set of acceptance criteria would be important for the particular PET manufacturer, but you apparently choose to have a more comprehensive COA for some of your customers that may need it. Each individual needs to establish those criteria that are important.

CHALY: Thomas Chaly from Northshore. On page 23, 1022, environmental and personal monitoring, environmental monitoring is crucial to maintaining aseptic conditions. Microbiological

testing of the aseptic workstation should be performed periodically. Can you clarify that more? Can you explain that, elaborate that?

AXELRAD: Sorry, what lines?

CHALY: Page 23, 1024.

URATANI: Do you want to clarify?

CHALY: How often do you have to do it and what do you expect from us?

URATANI: I think you should make your determination. You know, I would say maybe once every two weeks at least.

CHALY: Once every two weeks?

URATANI: Yes. Also, depending--yes, I think once every two weeks.

CHALY: Because you certify every six months the laminar flow hood from outside vendor and, you know, if we have to do this--

URATANI: No, I am talking about the microbiological monitoring.

CHALY: No, I am talking about the environment. I am talking about the laminar flow hood. You want to do that on a regular basis? Is that what you are saying?

URATANI: Not regular basis, periodically.

CHALY: How often?

KASLIWAL: I think you might want to refer to the USP chapter and that actually says weekly, believe it or not.

CHALY: I think that is a little too much. Weekly testing--

KASLIWAL: But I think the bottom line is you design your program that works for you. If you have established procedures--

CHALY: Can we have it established according to our SOP?

PARTICIPANT: [Not at microphone; inaudible].

AXELRAD: If that is all on contents and composition, we are going to take a very short, I hope five-minute break and then reconvene.

[Brief recess]

AXELRAD: I understand that some people have flights to catch, and what I think I would like to do is spend a few minutes on sterility and pyrogenicity which, I gather, hasn't been covered yet. Then I want to cover the IND research issue. Then we can go back and pick up any of the other issues in the guidance that haven't been covered yet, but I know that some of the people from AMI have flights to catch and so they would like to be

here for the IND and research discussion. So, if that is an okay plan, why don't we do sterility and pyrogenicity testing?

URATANI: Any comments on sterility and endotoxin tests?

AXELRAD: Somebody identified that but maybe they left.

BROWNLEE: I am Jan Brownlee, from SYNCOR. In the USP it says that if you are doing multiple runs in one day you can do one sterility test on, say, the first batch and that that would then indicate the sterility of the other batches done on that same day, assuming that all of the parts and all of the other conditions stay the same. Would it be possible then to do that with the production of PET drugs, like FDG? If you are doing three runs, to just do sterility testing on the first run that was done that day?

URATANI: I think you will have to submit it in your application and if it is approved, then that will be okay.

KASLIWAL: I think the key is it is possible to do that; I think we did write it that way, but which batch you will test has to be defined in your application. So, that batch has to

be defined, that you are going to do the very first batch or you are going to do the last batch. What you cannot do is today you are going to do the second batch; today you are going to--you can't do that kind of thing.

BROWNLEE: As long as we are consistent.

KASLIWAL: Right, and that has to be defined in your application.

BROWNLEE: The second question is that in the current proposed regulation you are saying that the sterility test has to be initiated within 24 hours of the run. Sometimes when you are doing a run on Fridays, this is a little bit impractical and in some cases puts the operators at risk because then they are going to have to handle very hot material within those 24 hours, whereas if they could wait--you know, they would have to come in on Saturday and do it too, but if they could wait until Monday since this is really a test that you are not going to have results for 14 days anyway, it is already in the patient, is there really any harm in waiting till, say, Monday to initiate that sterility test for the batch that was made on Friday? Could you wait until the next work day?

KASLIWAL: We were asking how long can you

wait.

BROWNLEE: It is not going to change the outcome. You can't recall it in either case.

KASLIWAL: Right. The schedule is something that is going to be approved as part of your application, but I understand your comment and I think we can look at that.

AXELRAD: We are going to have to talk to David Hussong, the sterility expert who was involved in writing this part of it, but we can look into that.

BROWNLEE: Okay. Another question we had is that it said that if the sterility testing fails you have to do immediate notification to the receiving facility. It has been our experience that rarely is it the product that is not sterile, usually it has been something in an operator's technique and, therefore, we would wonder if you couldn't do notification following investigation and determination of whether or not it is really the product that is not sterile or was it something else before you did notification. Could you wait until you have done your investigation?

URATANI: No, I think you should notify them right away. It might take you a while to do

the investigation to find out what is wrong, or you might never find out what is wrong.

BROWNLEE: Yes, but you have already probably got seven days. In either case, again, the outcome is going to be pretty much the same.

URATANI: We still think it is prudent for you to notify the receiving facility right away. Of course, maybe nothing can be done because it is already administered into the patient.

AXELRAD: You might be able to be on the lookout earlier for problems that might have arisen. I mean, the longer you wait the harder it is to follow-up.

BROWNLEE: You don't know at that point whether or not the product was not sterile.

DUFFY: Typically, when a sterility test comes out positive, usually specification is accomplished and that might be useful for the physician in looking for signs and symptoms and possibly prescribing an appropriate treatment.

BROWNLEE: Right. We do those things but, again, you are not going to get those results immediately and so you are going to notify the receiving facility but you are not going to have any real information for them until after you have

done your investigation.

DUFFY: You are correct on that point. Think of it just as limitations of the particular test.

BROWNLEE: Okay.

HUNG: I have a question about the pyrogen test on page 27. The guidance mentions the USP General Chapter 85, the bacterial endotoxin test, and I know that a 20-minute test is not mentioned in that particular chapter, although the 20-minute test is mentioned in chapter A23, the compounding of PET drugs. So, I am wondering whether chapter A23, specifically talking about the 20-minute pyrogen test, would be recognized by the FDA.

KASLIWAL: Yes, I recall a long discussion on that USP. I think our view is that the USP chapter 85, the full-fledged pyrogen testing, is the regulatory method. Now, if you want to do a 20-minute test for your own assurance, it is fine to do it but I am not sure what the regulatory significance is here.

DUFFY: Let me add a little bit of insight to that, you would establish in your application a set of acceptance tests, acceptance criteria procedures that describe the specification. That

constitutes what we refer to as the regulatory specification. Now, you may choose to use what we refer to as alternate tests provided that you have some demonstration that the test is essentially equivalent or better. So, if you have another method which might be more amenable to automation, is faster, possibly there is a cost implication but it is equivalent in terms of its capability, then it is appropriate to use that alternate method.

AXELRAD: You are asking us about a specific USP--

HUNG: Yes, I know.

AXELRAD: --and the question is what do we think about that in the context of what we know about PET.

DUFFY: I was trying to give it a more general spin. For A23 quick test, if you demonstrate it to be equivalent to the 85 test, that is fine.

AXELRAD: We can ask David about mentioning it in the guidance based on his knowledge of it too.

ZIGLER: Also, in the approved application for FDG, that includes a 60-minute test but also releases the product prior to the completion of

that test. So, is that another example of a place where you would put that in your application and then demonstrate it at that point?

DUFFY: That is correct. We will consider adding some wording.

ZIGLER: Thank you.

WATKINS: Len Watkins, from the University of Iowa. The levels that we test are 0.6 EU/ml, which approximates two orders of magnitude below the acceptable limit of 175. In a 20-minute test we are dealing with an exponential--if you can see it in 20 minutes it is still going to be well within acceptable limits. I think the 20-minute test should be accepted.

KASLIWAL: So, you think a 20-minute test while you have your 60-minute test is still going on?

WATKINS: Correct.

KASLIWAL: Okay.

WATKINS: We use this as release criteria. Twenty minutes is the normal time it takes to do most of the tests for FDG and you can do all the tests. You are just adding on 40 minutes totally unnecessarily because if the thing is going to be positive, it is going to show up in 20 minutes.

KASLIWAL: Yes, I think that is fine.

WATKINS: It doesn't make an unacceptable product; it may not be as good as you would like.

KASLIWAL: Right. I mean, you have two provisions not to do 20 minutes at all, and since you want to do 20 minutes, that is better than not doing it.

WATKINS: Several years ago we did some work, and I have mentioned this in previous meetings, particularly in FDG where you have laminar columns. These are very efficient at pulling out endotoxism. So, unless you have a huge amount it is not very likely you will have endotoxin contamination.

COOPER: On this subject, let us not forget that chapter 85 also has photometric tests that can be completed in 15 to 20 minutes.

WATKINS: I would like to make a comment on sterility. I have a paper where I have looked at 30 consecutive batches and have done bioburden studies, and in 28 out of the 30 I think there is absolutely nothing that shows up, and a minor amount in the other two. So, the amount of bacteria that are being exposed to the final filter is negligible. Then we are doing bubble point

tests to prove that the filter is okay. With the sterility tests afterwards we are concerned about times. Unless we do it the very second after we get the batch to make sure we get the shortest-lived species, this test doesn't really mean very much. We can still do it but I think testing it within 36 hours would be perfectly acceptable.

URATANI: I just want to make one clarification to the previous question with regard to sterility and whether you can just test the first batch. I neglected to say on your track record for sterility tests, if you have a good track record and what we are allowing here is also subject to review and approval. This is in agreement with what is in the USP.

SWANSON: Just a comment, you know, a lot of your release requirements address the things that need to be done prior to release, and they all say with exception of sterility. Certainly, since these requirements are going to be written for all PET drugs and we don't know what is going to happen down the line, it is going to be very difficult to complete the full official one-hour pyrogen test for many of the PET drugs, especially C-11 etc.

So, it is something again that our guidance document may want to get into and certainly consider looking back at some kind of shorter test methods, a photometric method or 20-minute release test, or something in there.

AXELRAD: Our guidance document can certainly recognize that there are other things out there that may, for various reasons, like shorter half-life, require a completely different system here, and we can certainly do that. One of the nice things about a guidance document is that it can be revised more quickly if one of these other drugs comes into more wide use, or when we identify issues associated with it the guidance document can be relatively easily changed to reflect that. We don't have to go through the whole rule-making process which takes a lot longer.

SWANSON: If you consider this easy.

AXELRAD: Yes, well, once we get it out there, changing it, hopefully, will not be quite as difficult as getting it out there in the first place.

BUDINGER: I am Tom Budinger, from Berkeley in San Francisco. I am worried about the last comment because there are some generators that

are even far more of a problem in terms of sterility. We haven't been using them recently. The likelihood is that we might start using them pretty soon. I-122 generator. So, now we are talking about a three-minute half-life from a 20-hour precursor. The 20-hour precursor is xenon-122, shipped from Canada, shipped across the country and it could even be shipped from Europe. We are familiar with the copper zinc generator. That is nine hours and--what?--ten minutes. Do I have that backwards? Anyway, I am making my point that there are generators other than the old rubidium generator that are likely to come into use. There are about 20 generators that one could conceive of using. So, I would hope that in the rules we could address that forthwith and not wait around until we have some problem with these generators because we know that they are there. We have all used them. They just aren't being used that much.

AXELRAD: What a perfect segue into the issue of research and INDs. I think we can address it forthwith by segue-ing right now into a discussion. This is written, as everybody has sort of recognized, with the understanding of FDG and

the few other more widely used--M13 and sodium fluoride that are more widely used PET drugs now.

I think there is the whole other question about whether these kinds of requirements should be the same requirements that are imposed on drugs that are just in research versus drugs that are going to be studied in humans under an IND. We are not really prepared to discuss here the whole issue of which drugs are going to be done under RDRC and which drugs need to be done under IND. For application requirements that is a separate discussion, but what I would like is to hear from you all about the problems that applying this to research drugs or drugs under an IND would present to you, that are different or unique and different from the problems that we have already discussed this morning and earlier this afternoon about the guidance as it applies to FDG and other drugs that we can perceive being approved for relatively widespread use in the near future.

CONTI: I made a comment earlier and I want to just repeat myself a little bit, and also expand on it. I think the CGMPs, as such and probably with subsequent modifications, are going to be applicable to drugs that have a fairly

established track record of production across facilities, with widespread familiarity with intimate details of synthesis and many publications on the clinical utilization.

I think that scenario is very different than the new radiopharmaceutical that may be under an IND, being investigated at one or maybe two or three institutions who all use a different synthetic procedure; the control systems and suppliers are all different, and things like this, where conducting those clinical trials under any type of rigorous CGMP protocol would just not work and, frankly, has not been necessary over the many years that we have been doing these types of radiotracers under IND.

I think we more or less feel, as a committee at least and certainly the audience can participate, but I think the committee basically has a consensus that when we are at the point where we are going to write an NDA for a new pharmaceutical it would be reasonable for us to be coming into some sort of CGMP compliance in order to achieve that NDA goal, and that may be in a late Phase III trial with a new radiopharmaceutical or something of that nature where you are now dealing

with multiple institutional trials and there needs to be some standardization in terms of the chemical process, how the material is handled etc., etc.

But before that, there really is no need, at least in our opinion, to have a CGMP type process when, in fact, you have so many variables. That is a rather general statement but I think it is pretty much true across the board.

AXELRAD: Let me just turn that around and say perhaps when you know so little about the process and you have so many variables, that would be a more appropriate time to have some sort of CGMP because you don't know what is happening; you don't know how the product is going to behave; you don't know whether there are problems that could be associated with getting mix-ups in components and things like that.

Also, let me sort of turn it around and say, okay, are you proposing nothing, that there would be no GMPs for research INDs, or could you foresee some modified form of GMPs, that there ought to be perhaps some kind of controls on research and INDs, maybe not here but something? If so, what would that look like?

CONTI: I think, again, we are in

agreement that we have some sort of control. There are some sort of criteria that we would have to be able to provide this for human use. As I said, we have a very long track record of using radiopharmaceuticals under IND for many, many years in a relatively safe environment, I would think, and FDA has participated, clearly, in approving those INDs and has cone a fairly good job in terms of weeding out those that are not necessarily safe over the years.

I think, again, we are also looking at it in a very focused fashion when we are doing this new drug development. We are looking more carefully at processes in order to improve production capability. We are trying to optimize. We are trying to determine whether there are side effects of these drugs under these types of scenarios and under an IND.

So, I think we have a little bit different focus compared to the routine clinical use of a radiopharmaceutical that is an approved drug. So, I think we agree that there needs to be some level, but certainly not to the level that we are talking about for these approved pharmaceuticals.

DUFFY: Let me offer just a little bit of

explanation. Go ahead.

CROFT: I am Barbara Croft, from NCI. I wanted to say we are starting a virtual drug company. So, we are quite concerned about this because we will be paying, the U.S. taxpayer will be paying for toxicology, pharm. tox., things of this kind for these drugs. Now, at what stage do we say this is the drug that will actually given--I hate the word drug, by the way, in connection with these things, but this is the drug that will actually be given to the patients, and step across that line from whatever this is that is not CGMP into the CGMP world and still have the proof that what we just spent our money on and your money on actually is the material that is going to go in the vial in the real process down the line in Phase I and Phase II testing? It worries me a lot to say sure, it is fine; you can go non-CGMP up to a certain point, but how do we know it is the same stuff, and how will you know, and how will you assure us that you know that it is the same stuff? If we can't prove it is the same stuff, we have to start over. And, I would rather start from the first correctly than staring over because starting over costs twice as much money, maybe three times.

BARRIO: Barbara, the point is not related to the quality of the product you will be injecting into humans. Definitely--

AXELRAD: Why isn't it? I don't understand why you say that it has nothing to do with the quality of the drug.

BARRIO: Well, let me raise some points. For example, RDRC and IND requirements at this point indicate that you have to describe your process well. You have to indicate your quality control, chemical purity, radiochemical purity and all the variables that are necessary, and they are normally described in USP monographs, for example. But, for the most part, the synthesis of these radiopharmaceuticals under RDRC or, perhaps less likely, under IND or advanced INDs are not optimized yet.

I don't know of anybody who will synthesize a compound for the first time and produce two curies of it. We only need ten millicuries to do a few studies. And, we can discover after, you know, a few human studies that this is not a compound we would like to use. Then we have to jump to a different one, and so on and so forth, until in this family there will be one or

two that we may eventually use. Then, these are the ones that will progress into the IND system. Then appropriate clinical trials are conducted and the synthesis is optimized then, at that stage, we apply the CGMPs in full as they are applied here.

We are not saying that CGMPs shouldn't be applicable. What we are saying is that CGMPs should not be applicable in the same way that they are applicable to drugs in the clinical domain. I think that is the only thing I am saying. In no way, absolutely no way, would we want to compromise the quality of a compound. I think that these CGMPs should, absolutely should assure the quality of the compound to be the highest possible.

HUNG: To take the same kind of approach to a non-PET radiopharmaceutical in terms of IND applications, as long as we just follow the IND application package, the requirements and that kind of stuff, there is really no need to requirement the CGMP for that.

AXELRAD: There are people in the audience I think, radiopharmaceutical manufacturers who could speak to this and I would appreciate it if anybody would be willing to talk to it. But CGMPs do apply to INDs for commercial

radiopharmaceuticals. You don't have a master production record and a batch--you don't have all the elaborate kinds of things that you have when you get an approved drug product with a finished dosage form, but there is a modified form of CGMP that is put in place for those radiopharmaceuticals and that is what we are trying to get at here, what is the modified form of CGMPs.

I think we felt that a lot of language that we put in the regulations and in the guidance document that says it depends on what you are doing; it depends on the process; you have to identify the criteria parameters yourself--all of those things are things that are specifically designed to build in enough flexibility that could apply so you can decide what kinds of controls are necessary if you are doing a bunch of different small batches of research drugs, or you are doing an IND batch, or whatever. It gives you the sort of flexibility in the regulations and the guidance that allows you to scale down the GMPs to the kind of operation that you are doing.

But I would really like to hear from anybody in the audience who would like to speak to how they do it for a commercial radiopharmaceutical

manufacturer.

CLANTON: Jeff Clanton, Vanderbilt University. One thing that seems to be disconnected here is that they are talking about physician-sponsored INDs and you are talking about commercial-sponsored INDs, a really different ball game.

AXELRAD: But I am talking about a PET production facility and I don't understand what that has to do with the quality of the product. The IND GMP requirements are designed to ensure that there is a good quality product that is injected into the patient, the first time it is injected into people. Commercial manufacturers may be making very small amounts of radiopharmaceuticals or experimenting with many different kinds of radiopharmaceuticals to decide which one they want to go forward with and get an approved application. They put certain controls in place to ensure the quality of the product that they are producing, and the question is what are those controls, and why are they not applicable if it is a PET production facility that is doing the same thing, regardless of who is sponsoring the IND? We are not really talking about who sponsors

it.

Again, I am not talking about whether you can or whether it can be, the question is what kinds of controls are necessary to ensure the quality of that product regardless of who is sponsoring the application.

BARRIO: This problem doesn't apply to us, from what I know. I think it would be the first time that academia would be subject to a situation like this.

AXELRAD: All drugs are under this provision. In fact, drugs used for other purposes, not just diagnostics, things like for urologic, if you even have a physician-sponsored IND using an already marketed drug, the marketed drug has its GMPs covered by the manufacturing, but if you are going to make it yourself you have to provide those controls in your laboratory. It doesn't have to be for an imaging agent.

CLANTON: [Not at microphone; inaudible].

BARRIO: Not through CGMP in an academic environment. That is a different situation. But let me point to one issue. For example, rarely, if at all, do we use automatic systems when we start a process of development of PET pharmaceuticals.

Number one. We use manual, semiautomatic systems that we can adapt to improve or change completely soon enough. It is not an established process many times. We are trying to improve the yield or modify it, or whatever, but we absolutely always check--we always did that, check the quality of the final product before this is injected in humans.

I think what makes it difficult, Jane, to apply it in a way that we do it with established radiopharmaceuticals is that we may be also in the process of modifying something after it goes into operation, going from semiautomatic to automatic and certain things like this that, you know, will need to be changed or may need to be changed or will be changed. Yields will be lower initially and we will try to speed it up, depending on what kind of compound we have. Then the process is not necessarily stable in the way we design; the quality doesn't change. I think it is an issue of process more than of quality of the product.

WALTZ: Debbie Waltz, from the University of Pennsylvania. I think I speak a lot from my background in the pharmaceutical industry where I spent 17 years in quality assurance, and I have been at Penn for a relatively short period of time,

about eight or nine months now. So, it is interesting to me, the difference between an IND if it is investigator sponsored or pharmaceutical sponsored because the whole point of the IND, the main components of the IND are sufficient animal model characterization for the toxicity to show that it is safe to go into humans, and the CMC section, which is your manufacturing controls. The CMC section, those requirements are to adhere to the spirit of GMPs, manufactured under GMP conditions in a GMP, you know, facility that is sort of honoring the cleanliness, the characterization of the drug, the ability to reproduce the drug, the same drug. You know, you need to have the stability well characterized of the drug before you go into man. So, the fact that you are adjusting your process to produce the same compound twice, you are still working those aspects out, at that point you are probably not ready for the IND yet. I mean, until you can do it twice.

Then, you know, the whole point of the IND is to have your standards put down, assembled into the document to give the FDA the opportunity to comment back, yes, we agree that this is robust or, no, it is not.

BARRIO: I think this has nothing to do with how robust the system is, it is the fact that you don't care to go and increase your yield to limits that are not necessary at the time, and you don't care about having an automatic system for the synthesis for a radiopharmaceutical for you don't know how long you are going to study.

WALTZ: I mean, it comes down to you are trying to produce a drug that is safe to put in humans.

BARRIO: Right, and it is.

WALTZ: To the extent that you are able to do that, those are the elements that go into making [not at microphone; inaudible].

BARRIO: That is absolutely right.

CONTI: One of the things we have to learn around here is that we do things a little bit differently than traditional pharmacy. That is why for years we have been arguing that we are not really drugs; we are different. That is why we test all of our drugs at the end. That is different than lot or batch testing. We are different. When that sinks in we will be able to move ahead.

WALTZ: I understand that we don't have a

pharmacologic effect.

CONTI: You need to spend more than eight months at Penn.

KEPPLER: I do want to make one comment, and I think Jane may have missed it earlier, and I haven't seen this but if the ICH document for GMP really has this statement that--the woman from SYNCOR may be able to help me, that process validation is not necessary when you are able to test the full output. Certainly, with these compounds that is the issue. You are running an HPLC on the full output. So, to validate changes in your process before you know whether or not they are going to work, that is where the problem comes in, especially when you are doing full output testing.

HARTIG: My name is Per Hartig. I come from the Uppsala University Pet center. To me, I think this discussion about different regulations for big and small, company or routine is a little bit confusing because, of course, when you are starting you will have a strategy for how to validate your tracer, and that is if it is endogenous compound, a new drug or whatever it is. You have to have some knowledge about what it is

doing. You have to test it in animals. Of course, you have to put up all the quality procedures so that you will have the same safety as when you are giving FDG for the thousandth time as when you are giving this new drug for the first time. I think it is absolutely our responsibility to put up the same demands on the new compound as we do for one that we have done for ten years.

CHALY: Thomas Chaly, from Northshore University Hospital. There are a lot of problems with research compounds. First of all, the materials are not standardized. I can take an example. We have been making fluoro for a long time. There are people who use different methodologies and there are probably nucleic substitutions. There are no established black boxes available to make these compounds.

So, this is not standardized. We are still trying to improve the yield. If you write something right now, tomorrow you are going to change that. So, having CGMP for these kinds of compounds will be very difficult.

AXELRAD: I think one of the problems with this seems to be semantics. To you, you seem to think--collectively, everybody who is commenting on

this, that CGMPs means final release specifications, in-process specifications, process validation of every step, process validation of the software, process validation of the box. For IND drugs, obviously, since you don't have a synthesis box; since you don't have a final product, we mean something other than that. The question is, is there a way of closing in? I mean, I am sure we will have to have at least one more meeting and maybe several, but I need you all to come and suggest to us something short of nothing, short of just trust us; it has been working fine all along. What is there, somewhere in the middle, that you would be willing to agree that everybody should be held to in terms of GMPs for research and INDs?

CHALY: Suppose a lot of people are using chloral hydrate and we should establish what can be done for that particular compound. Maybe another compound not many people are using, maybe one or two institutions are using this. So, what are we going to do with those kinds of compounds?

AXELRAD: Well, the patients who are taking those compounds are just as entitled to getting a quality product as the people who are taking FDG.

CONTI: And the physicians who are giving it believe it is a quality product.

AXELRAD: Drug companies who are making their drugs and testing them under INDs, the deal is that we don't just trust everybody to do the right thing and make sure there is a quality product. We make sure through regulations that everybody is making something that is a quality product.

CHALY: I think FDA has to trust these institutions like the way you trusted us for FDG for the last so many years. So, we are coming out with new things for these compounds and we will improve it, and at that time we should have a CGMP.

BARRIO: Jane, you are absolutely right. I think in great measure what is going on here is semantics. I don't like the implication coming from the fact that if we don't do certain things the quality of our products is going to be poor or low. This is absolutely, completely not the argument.

I remember that when we started all these discussions about CGMPs, the agency got the impression that the PET community was just mixing and injecting people without having any quality

control simply because we rejected the notion of CGMPs that was so foreign to us. I think the same implication exists here. Like, you know, you don't want to subject yourself to CGMPs, therefore, you want to inject anything. But that is not true; absolutely not true. There is not a single researcher I know, and I am going to mention this with great passion because we have done this for the last 25 years, there is not a single researcher I know that will inject second-class compounds of radiopharmaceuticals to people. Certainly, we are not lawyers. We are bad lawyers, if anything. We don't want to subject ourselves to certain kind of things, but this is not the danger; the danger is not to say that we don't know what we are injecting, and this is something that should be clear.

I think Jane is absolutely right. I think some implication of my comments and ones made over here is that, well, then the quality of the product can be compromised. Please, please be assured that this is not the case. The only thing we are saying is that if we are going to apply CGMPs during the process of development, we have to have the flexibility you just mentioned. We don't have an

automatic system. We don't have a bunch of things that probably would be inappropriate to validate, or to check, or monitor in comparison to something we have seen for 25 years and is everywhere for clinical use. I guess that is what the point is.

AXELRAD: But maybe if you could share with us what you do have, I mean, what do you have and what do you use to assure yourself of what you just said, which is that products are of high quality and you are not just mixing up anything? What do you use to assure yourself of that? Perhaps if we could get a better understanding of what you, yourself, are relying on to make the statement that in, and of itself, is the GMP.

BARRIO: Anything you do for FDG, any quality control you perform for FDG you perform with any radiopharmaceutical that you will inject into people under RDRC, IND or whatever. Those are exactly the same requirements, exactly the same idea.

PARTICIPANT: On 100 percent of what you make.

KEPPLER: Yes, I think that is the issue, Jane. I don't think we have, especially on this issue, moved any further than we were at the very

start. I think that the community, certainly the folks that are taking this position, don't feel that all of the process validation and the process control steps are going to impact the quality of the drug. So, that is why we are resistant to those things because they wouldn't allow us to develop the drugs.

You know, on a large scale we can understand the need for process controls, and that is why we have gotten as far as we have gotten, but through this process we are testing the full output of every batch for sterility, pyrogenicity, drug quality, purity through HPLCs. I mean, everything is tested on every ounce before it goes into a patient.

AXELRAD: What about component control? Forget about process validation for now and set that aside. If you are making 10 or 12 different drugs--I have heard many, many times over the years that if you don't put in the right stuff you don't get FDG and you do a test at the end to make sure that you have FDG and that there is a certain kind of purity, and all that. So, that is not a problem. But what about some of these other drugs and tracers, not just the radioactive part of it

but also the ligand that you are hooking it to, when you are building one of these things, isn't there more of a need, especially if you are doing a bunch of different ones, to control the compound and make sure that you are getting what you think you are getting because in some of these cases it might be that you don't produce the same thing, and it could have an adverse effect on the patient, or the ligand doesn't take the drug to where you want, and either it has a safety effect or it doesn't work the way you expected? Do you do a little more compound control when you are making a whole bunch of other drugs?

SWANSON: I will tell you what we do. We follow the USP chapter, and in there, there is a control component. It is not nearly to the extent of what you require for CGMPs but, basically, if you look at the USP chapter, it has adopted the principles of CGMPs and I think we would all agree with that. It just does not go to the extent of validation that you have outlined in the CGMP process. But that is how we have been doing it. That is how RDRC approves it. We need three validation runs and have to demonstrate that we are able to produce this compound before we are allowed

to go into human use. They have the appropriate radiochemical purity, everything is outlined in the USP chapter. That is why we wrote the chapter to begin with.

URATANI: Well, FDA does recognize that for investigational drugs, the drug product, the production process has not been fully developed and is not established yet. So, with regard to the CGMP requirement for investigational drugs, it is much less than for an NDA or ANDA. Basically, we are asking that your investigational drug is produced in a qualified facility, using qualified equipment, and we also realize that at the early stage of an IND you will have very little data on validation. We understand that. However, towards the later stage of a clinical trial, like the later stage of an IND, you might have accumulated enough data and maybe enough batches so that you will be able to have a procedure to validate your process. So, we are not asking for the full manual that is required in an NDA and ANDA.

BARRIO: I think we are saying the same thing.

CALLAHAN: It goes a little further than that, to where we will never get to an IND. There

is no plan to use this as a diagnostic agent. We may study six or a dozen or thirty human volunteers on a PET drug in conjunction with some other protocol. So, we will never get to that point. So, we have to rely almost entirely on the end product testing and USP chapter as described. I mean, that is what we submit. We will never get the fully validated production because by the time we have done half a dozen subjects that protocol is done; we have answered the question; we have provided the data and we will go on to the next one. So, it gets worse than just the IND, early stages of IND versus late stages. These projects have a half-life of a few months to a year, and then they are gone. And, those are PET drugs so they come under this broad discussion. So, that is another level of scrutiny. I support, as Dennis and I have discussed already, using the USP chapter model for research applications. End product testing as outlined, addressing the other issues of components and environment I think are valid almost as written.

AXELRAD: I think we have to explore the differences of what we put in the guidance or what we are contemplating for GMPs and how it is

different from the USP. I think that in some cases we felt that the USP chapter was so vague as to allow anybody to do just about anything.

So, the question is whether when you say we are all following the USP chapter, does that mean you are all doing all different things, or is there some minimum level of quality that you are being held to by following the chapter?

SWANSON: It goes into a fair amount of detail as to the kinds of testing that is required in validation studies, and routine batch quality control. It also goes into a fair amount of detail as to what is required for testing of components.

AXELRAD: I think we need to look at that more carefully again and try and see where we went beyond the USP and where it is causing problems in two different worlds really, on the one hand, in the sense of what we expect to be the widely used NDA approved drugs, and also then for the other drugs that are used under RDRC.

CALLAHAN: It is a balance issue. I think the GMPs, as discussed today, are very front-end loaded, and I think the USP and how most of us practice is very back-end loaded. That is the problem. Until we find a balance.

URATANI: I guess I also have a question. Can you tell me how many of those IND drugs will actually become an NDA or ANDA?

PARTICIPANTS: Zero.

URATANI: They have no commercial application?

PARTICIPANTS: Zero.

URATANI: And what is the difference between research conducted under RDRC and IND PET drug?

CALLAHAN: Well, our understanding of that is what we know about the ligand itself. If we know human pharmacology of the molecule that we are labeling with a PET tracer, and a few other things regarding dosimetry, then that is suitable for certain types of initial human investigations under RDRC. If we were to have a completely new molecular entity for which we do not know the human pharmacology, for which there is no human experience of the non-radioactive form, then we are probably going to be squeezed into the IND mode, kicking and screaming all the way. But that is how I understand it. Our RDRC essentially only deals with PET protocols. In this day and age, I think RDRCs are really only amenable to PET types of

studies and maybe a few other, you know, radioactive water or radioactive titrated water, or something. It is really ideally suited to PET research.

SWANSON: To expand on that, under an RDRC we are only allowed to approve research studies where a radioactive drug is being used to evaluate physiology, pathophysiology, metabolism. We are specifically not permitted to conduct a clinical trial under an RDRC approval, a clinical trial being a study to determine the safety and effectiveness of that radioactive drug for the diagnosis of a specific disease or condition. So, if you go back and look at the RDRC requirements, they are very specific as to the type of research that we can conduct under an RDRC approval.

But it is also very important--you know, what I am hearing is you are saying, well, we will address this through an IND application but those of us who are in charge of RDRCs have to have some understanding for what basis do you want us to allow these radioactive drugs to be used in those types of studies. Please do not take that away from us because that is a particularly important area of research and, as pointed out, those drugs

never-ever get developed for commercial use.

URATANI: The RDRC drugs or IND?

SWANSON: The RDRC drugs.

URATANI: So, all the RDRC drugs will never become an IND--

BARRIO: No, no, no.

PARTICIPANTS: No.

SWANSON: They could, but as per the RDRC regulations, if we wanted to pursue them for the diagnosis of a disease or a condition, then we would have to go the traditional IND route.

CROFT: One in a hundred or one in five hundred may pass to an IND. It is going to be a very small number.

HUNG: You have a very short half-life. Oxygen-15 is two minutes. There is no way you are going to make it commercially available.

AXELRAD: Let's have one last comment on this subject and then we will see if we can pick up on anything else that anybody wants to comment on.

CHALY: I just want to say that we are not picking up any drugs on the street to do this research. We are looking into established carbons and then we label it and we look at the toxicity and we do animal studies before we do anything

else. So, it is going through a lot of process before we inject it into a patient. We are not just labeling any compound and taking it to the patient. So, there is a lot of process going on behind this. So, there is a lot of safety consideration before we inject it into the patient.

AXELRAD: Let's pick up on any other topics that we haven't addressed before we close here.

SWANSON: If I may comment, one that I did want to get out there deals with laboratory controls, and there is a part of the CGMPs and the regulation, actually, that specifies that PET centers must establish and document the sensitivity, specificity, reproducibility and accuracy of all test procedures. You know, I guess I get real concerned about, for example, we use narrow range pH paper to measure the pH of a product. Do I have to establish sensitivity, specificity, reproducibility and accuracy of that procedure? All I am saying is the guidance I think is very deficient in that area at this point.

LEUTZINGER: I agree; I agree.

URATANI: I guess you also should know that there is a difference between verification and

validation. If you are using a USP method, you only need to verify that it works under the conditions of actual use. Validation will be a much more involved process. It could be some methods that you develop and you have to go through the whole program to demonstrate specificity, linearity and other stuff specified in USP.

MOSLEY: Another topic, please, training. Can you give us some guidance on what constitutes training for personnel in a PET production facility?

URATANI: Well, I guess if you have personnel who is trained to do aseptic processing, in our guidance we did say that you will have to document what type of training has been given. It doesn't have to be a class that he or she has to take in a university or some professional organization. You can train that person in-house and document it. As far as aseptic processing is concerned, there may certainly be a requirement for the filtration process and assembly set up, using media instead of using the product to demonstrate that that person who is handling it is able to do it sterilely.

MOSLEY: Specifically, is there a written

text that I can cite for my senior management when trying to suggest that faculty or people in an academic PET center are adequately trained? Is there a checklist of criteria that are written that I can use?

KASLIWAL: I think one is production operation. You know, if the person is performing production, if you are training them, that is one aspect. Testing is another aspect, quality control. So, those two and some of the training that Brenda described would be part of production.

AXELRAD: I don't think we have a checklist, in answer to your question.

MOSLEY: Is there another guidance document that you can refer me to?

AXELRAD: I don't even know of much in the way of guidance on training. I mean, even GMPs for regular drugs say make sure your people are adequately trained to do whatever it is they are going to be doing.

MOSLEY: I just need something concrete so that when I go into an academic site I can say to my management that, yes, indeed, the staff is trained and here is why.

AXELRAD: It would be really good if you

would develop it and we could adopt it. You are going around to 30 PET centers. You would be in a good position to be able to help us define what you think is adequately trained.

SIMPSON: Norm Simpson, Columbia University. The difficulty is, and we are getting into some of that now, who trains the trainer? Who is qualified to train the people that are being trained? So, at some point there has to be some delineation.

URATANI: I guess, for example, if you have a technician carrying out the FDG production, maybe the radiochemist or nuclear chemist will be the one who is training that person.

SIMPSON: And that is the problem. That is what I am getting into. My technicians actually do the routine production on a day to day basis, and when I have the senior faculty come in my technicians have to train them how to use that equipment and how to do those productions. So, in a classical sense, it is actually just the opposite of what is going on. So, who is really qualified to do the training? The people doing it on a day to day basis, who know the system inside and out? Or, the educated people that are at the M.D. or

Ph.D. level?

URATANI: Well, I would think it would be the person who does it on a day to day basis and be able to produce quality results.

AXELRAD: And also the vendors. The vendors ought to be able to train to some extent, or may offer training classes on the equipment that they are giving you.

CHALY: Thomas Chaly, Northshore. I think we have established chemists in this country who have undergone post-doctoral training in many educational centers, and they have trained a lot of junior chemists and technicians to do this in the last 20, 25 years. There are plenty of people trained to make these radiopharmaceuticals out there. I don't think there is any problem for training new ones.

I have another question. You are asking us to keep samples for 30 days after testing.

URATANI: What samples?

CHALY: FDG samples for 30 days.

URATANI: No, there are no reserve samples. It was taken out.

CHALY: I saw it in one of the notes there.

URATANI: No, it was taken out.

KASLIWAL: Can you clarify where we are asking that?

PARTICIPANT: That was deleted.

CHALY: Oh, okay. Sorry about that.

AXELRAD: Does anyone have any other issues that they want us to address or that they would like to comment on before we close? If not, thanks everybody for coming. We expect to do this again when we have an expanding audience, from what I understand. I don't know, maybe you will all go back and tell everybody, forget it; it isn't worth coming. But we will be looking for the written comments and I think you may be contacted, some of you may be contacted because I think we have identified some of you, from your interest in this, as being able to provide us information that may help us as we go forward on the document. So, we may contact some of you individually to get some additional information or follow-up on your comments. Thank you.

[Whereupon, at 3:45 p.m., the proceedings were concluded.]

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